L Number	Hits	Search Text	DB	Time stamp
1	580	((544/290) or (544/287) or (514/266.3)).CCLS.	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/11/26 15:43

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=> s hedgehog? (l) pathway?
          2719 HEDGEHOG?
        284175 PATHWAY?
L1         550 HEDGEHOG? (L) PATHWAY?

=> s normal?
L2      941844 NORMAL?

=> s l1(l)l2
L3         110 L1(L)L2

=> s patched?
L4         865 PATCHED?

=> s l3(l)l4
L5          41 L3(L)L4

=> d l5 1-41 bib,ab
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L5 ANSWER 1 OF 41 CAPLUS COPYRIGHT 2003 ACS
AN 2003:366249 CAPLUS
TI Inhibition of Epithelial Ductal Branching in the Prostate by Sonic Hedgehog Is Indirectly Mediated by Stromal Cells
AU Wang, Bu-er; Shou, Jianyong; Ross, Sarajane; Koeppen, Hartmut; de Sauvage, Frederic J.; Gao, Wei-Qiang
CS Department of Molecular Oncology, Genentech, Inc., South San Francisco, CA, 94080, USA
SO Journal of Biological Chemistry (2003), 278(20), 18506-18513
CODEN: JBCHA3; ISSN: 0021-9258
PB American Society for Biochemistry and Molecular Biology
DT Journal
LA English
AB Sonic **hedgehog** (Shh), a vertebrate homolog of the Drosophila segment-polarity gene **hedgehog**, has been reported to play an important role during **normal** development of various tissues. Abnormal activities of Shh signaling **pathway** have been implicated in tumorigenesis such as basal cell carcinomas and medulloblastomas. Here we show that Shh signaling neg. regulates prostatic epithelial ductal morphogenesis. In organotypic cultures of developing rat prostates, Shh inhibited cell proliferation and promoted differentiation of luminal epithelial cells. The expression pattern of Shh and its receptors suggests a paracrine mechanism of action. The Shh receptors Ptc1 (**Patched1**) and Ptc2 were found to be expressed in prostatic stromal cells adjacent to the epithelium, where Shh itself was produced. This paracrine model was confirmed by co-culturing the developing prostate in the presence of stromal cells transfected with a vector expressing a constitutively active form of Smoothened, the real effector of the Shh signaling **pathway**. Furthermore, expression of activin A and TGF-.beta.1 that were shown previously to inhibit prostatic epithelial branching was up-regulated following Shh treatment in the organotypic cultures. Taken together, these results suggest that Shh neg. regulates prostatic ductal branching indirectly by acting on the surrounding stromal cells, at least partly via up-regulating expression of activin A and TGF-.beta.1.

L5 ANSWER 2 OF 41 CAPLUS COPYRIGHT 2003 ACS
AN 2003:329403 CAPLUS
TI Identification of a small molecule inhibitor of the hedgehog signaling pathway: Effects on basal cell carcinoma-like lesions
AU Williams, Juliet A.; Guicherit, Oivin M.; Zaharian, Beatrice I.; Xu, Yin; Chai, Ling; Wichterle, Hynek; Kon, Charlene; Gatchalian, Christine; Porter, Jeffery A.; Rubin, Lee L.; Wang, Frank Y.
CS Curis Incorporated, Cambridge, MA, 02138, USA
SO Proceedings of the National Academy of Sciences of the United States of America (2003), 100(8), 4616-4621
CODEN: PNASA6; ISSN: 0027-8424
PB National Academy of Sciences
DT Journal
LA English
AB The link between basal cell carcinoma (BCC) and aberrant activation of the **Hedgehog** (Hh) signaling **pathway** has been well established in humans and in mouse models. Here we report the development of assays, including two novel in vitro BCC models, which allowed us to screen for Hh inhibitors and test their validity as potential treatments for BCC. We identified a novel small mol. Hh inhibitor (CUR61414) that can block elevated Hh signaling activity resulting from oncogenic mutations in **Patched**-1. Moreover, CUR61414 can suppress proliferation and induce apoptosis of basaloid nests in the BCC model systems, whereas having no effect on **normal** skin cells. These findings directly demonstrate that the use of Hh inhibitors could be a valid therapeutic approach for treating BCC.
RE.CNT 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 3 OF 41 CAPLUS COPYRIGHT 2003 ACS
AN 2003:135115 CAPLUS
TI Therapeutic efficacy of sonic hedgehog protein in experimental diabetic neuropathy
AU Calcutt, Nigel A.; Allendoerfer, Karen L.; Mizisin, Andrew P.; Middlemas, Alicia; Freshwater, Jason D.; Burgers, Monica; Ranciato, Rigel; Delcroix, Jean-Dominique; Taylor, Frederick R.; Shapiro, Renee; Strauch, Kathy; Dudek, Henryk; Engber, Thomas M.; Galdes, Alphonse; Rubin, Lee L.; Tomlinson, David R.
CS Department of Pathology, University of California at San Diego, La Jolla, CA, 92093-0612, USA
SO Journal of Clinical Investigation (2003), 111(4), 507-514
CODEN: JCINAO; ISSN: 0021-9738
PB American Society for Clinical Investigation
DT Journal
LA English
AB **Hedgehog** proteins modulate development and patterning of the embryonic nervous system. As expression of desert **hedgehog** and the **hedgehog** receptor, **patched**-1, persist in the postnatal and adult peripheral nerves, the **hedgehog pathway** may have a role in maturation and maintenance of the peripheral nervous system in **normal** and disease states. We measured desert **hedgehog** expression in the peripheral nerve of maturing diabetic rats and found that diabetes caused a significant redn. in desert **hedgehog** mRNA. Treating diabetic rats with a sonic **hedgehog**-IgG fusion protein fully restored motor- and sensory-nerve conduction velocities and maintained the axonal caliber of large myelinated fibers. Diabetes-induced deficits in retrograde transport of nerve growth factor and sciatic-nerve levels of calcitonin gene-related product and neuropeptide Y were also ameliorated by treatment with the sonic **hedgehog**-IgG fusion protein, as was thermal hypoalgesia in the paw. These studies implicate disruption of **normal hedgehog** function in the etiol. of diabetes-induced peripheral-nerve dysfunction and indicate that delivery of exogenous **hedgehog** proteins may have therapeutic potential for the treatment of diabetic neuropathy.
RE.CNT 48 THERE ARE 48 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 4 OF 41 CAPLUS COPYRIGHT 2003 ACS
AN 2003:65407 CAPLUS
DN 138:318284
TI Sonic hedgehog in normal and neoplastic proliferation: insight gained from human tumors and animal models
AU Wetmore, Cynthia
CS Department of Pediatrics and Adolescent Medicine, Program in Neuro-oncology, Division of Pediatric Hematology/Oncology, Mayo Clinic, SW Rochester, MN, 55905, USA
SO Current Opinion in Genetics & Development (2003), 13(1), 34-42
CODEN: COGDET; ISSN: 0959-437X
PB Elsevier Science Ltd.
DT Journal; General Review
LA English
AB A review. Cancer arises when a cell accumulates multiple genetic changes that allow it to elude the highly regulated balance between proliferation and apoptosis that an organism employs to suppress inappropriate growth. It has become evident that malignant transformation of a cell or group of cells often involves **pathways** that are active during **normal** development but are inappropriately regulated in neoplastic proliferation. Signaling via the Sonic **hedgehog pathway** is crit. to vertebrate development and also appears to play an integral role in the initiation and propagation of some tumors of the muscle, skin and nervous system. Analyses of human tumors have revealed mutations in various components of the Sonic **hedgehog** signaling **pathway** that appear to result in the activation of this **pathway**, as inferred by the increased expression of the transcription factor, Gli1. Interestingly, a proportion of the human tumors and most of those arising in mouse models continue to express the **normal Patched** allele, suggesting the involvement of addnl. mol. events in the transformation of the haploinsufficient cells.
RE.CNT 76 THERE ARE 76 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 5 OF 41 CAPLUS COPYRIGHT 2003 ACS
AN 2002:860103 CAPLUS
DN 138:299400
TI The transcription factor Sox9 has essential roles in successive steps of the chondrocyte differentiation pathway and is required for expression of Sox5 and Sox6
AU Akiyama, Haruhiko; Chaboissier, Marie-Christine; Martin, James F.; Schedl, Andreas; de Crombrugghe, Benoit
CS Department of Molecular Genetics, The University of Texas M.D. Anderson Cancer Center, Houston, TX, 77030, USA
SO Genes & Development (2002), 16(21), 2813-2828
CODEN: GEDEEP; ISSN: 0890-9369
PB Cold Spring Harbor Laboratory Press
DT Journal
LA English
AB To examine whether the transcription factor Sox9 has an essential role during the sequential steps of chondrocyte differentiation, we have used the Cre/loxP recombination system to generate mouse embryos in which either Sox9 is missing from undifferentiated mesenchymal cells of limb buds or the Sox9 gene is inactivated after chondrogenic mesenchymal condensations. Inactivation of Sox9 in limb buds before mesenchymal condensations resulted in a complete absence of both cartilage and bone, but markers for the different axes of limb development showed a **normal** pattern of expression. Apoptotic domains within the developing limbs were expanded, suggesting that Sox9 suppresses apoptosis. Expression of Sox5 and Sox6, two other Sox genes involved in chondrogenesis, was no longer detected. Moreover, expression of Runx2, a transcription factor needed for osteoblast differentiation, was also abolished. Embryos, in which Sox9 was deleted after mesenchymal condensations, exhibited a severe generalized chondrodysplasia, similar to that in Sox5; Sox6 double-null mutant mice. Most cells were arrested as condensed mesenchymal cells and did not undergo overt differentiation into chondrocytes. Furthermore, chondrocyte proliferation was severely inhibited and joint formation was defective. Although Indian **hedgehog**, **Patched1**, parathyroid hormone-related peptide (Pthrp), and Pth/Pthrp receptor were expressed, their expression was down-regulated. Our expts. further suggested that Sox9 is also needed to prevent conversion of proliferating chondrocytes into hypertrophic chondrocytes. We conclude that Sox9 is required during sequential steps of the chondrocyte differentiation **pathway**.
RE.CNT 47 THERE ARE 47 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 6 OF 41 CAPLUS COPYRIGHT 2003 ACS
AN 2002:756600 CAPLUS
DN 138:101095
TI Identification of indian hedgehog as a progesterone-responsive gene in the murine uterus
AU Takamoto, Norio; Zhao, Bihong; Tsai, Sophia Y.; Demayo, Francesco J.
CS Department of Molecular and Cellular Biology, Baylor College of Medicine, Houston, TX, 77030, USA
SO Molecular Endocrinology (2002), 16(10), 2338-2348
CODEN: MOENEN; ISSN: 0888-8809
PB Endocrine Society
DT Journal
LA English
AB Progesterone (P4) plays a central role in **normal** uterine function, from embryo implantation in endometrium to establishment and maintenance of uterine quiescence during pregnancy in the myometrium. Considering its diverse physiol. effects on female reproductive function, rather little is known about downstream events of P4 action. Recent progress in differential screening technologies facilitated identification of such inducible genes. We used uteri of wild-type and progesterone receptor null mutant mice as a starting material and screened for differentially expressed genes by medium-d. cDNA expression array. Here, we report that the expression of the morphogen, Indian **hedgehog** (Ihh), is rapidly stimulated by P4 in the mouse uterus. The level of Ihh mRNA is induced within 3 h, after a single administration of P4 to ovariectomized mice. The induced Ihh mRNA and protein were localized to the luminal and glandular epithelial compartment of the endometrium. During pseudopregnancy, the Ihh mRNA level was transiently increased in the preimplantation period and d 3 and d 4 post coitum and then decreased rapidly at d 5 post coitum. Furthermore, the expression profile of **patched**-1, **hedgehog** interacting protein-1, and chicken ovalbumin upstream promoter-transcription factor II, genes known to be in the **hedgehog** signaling **pathway** in other tissues, followed the expression pattern of Ihh during the preimplantation period. Our results suggested that Ihh is regulated by P4, and the Ihh signaling axis may play a role in the prepn. of the uterus for implantation during the preimplantation period.
RE.CNT 55 THERE ARE 55 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 7 OF 41 CAPLUS COPYRIGHT 2003 ACS
AN 2002:649762 CAPLUS
DN 138:87090
TI Differential Requirements for Shh in Mammary Tissue and Hair Follicle Morphogenesis
AU Gallego, Marta I.; Beachy, Philip A.; Hennighausen, Lothar; Robinson, Gertraud W.
CS Laboratory of Genetics and Physiology, National Institute of Diabetes, and Digestive and Kidney Diseases, Bethesda, MD, 20892, USA
SO Developmental Biology (Orlando, FL, United States) (2002), 249(1), 131-139
CODEN: DEBIAO; ISSN: 0012-1606
PB Elsevier Science
DT Journal
LA English
AB Sonic **Hedgehog** (Shh) is a secreted morphogen that directs patterning and cellular differentiation through binding to its receptor **Patched** (Ptc). It is required for the development of skin-derived organs, such as hair, whiskers, and teeth. The mammary gland is a skin-derived organ that develops mainly during adult life in which Shh is expressed from puberty to lactation. We have investigated the role of Shh in mammary gland morphogenesis and differentiation by two transplantation approaches. Since Shh-null fetuses die at late embryogenesis, we transplanted Shh-null mammary anlagen into cleared fat pads and under the renal capsule of wild type host mice. Pregnancy-mediated functional differentiation of Shh-null mammary epithelium was indistinguishable from wild type transplants, while hair follicles derived from cotransplanted skin only developed in wild type transplants. Transplants of Ihh-null anlagen also developed **normally**. To assess the mol. consequences of Shh deletion in mammary tissue, we compared mRNA levels of **patched** 1, a target gene of **Hedgehog** signaling, in Shh-null and wild type mammary epithelial transplants. No redn. of Ptc1 transcripts was obsd. in Shh-null mammary tissues. Our results demonstrate that neither Shh nor Ihh is required for mammary gland morphogenesis and functional differentiation, suggesting that the two members of the **Hedgehog** family may have redundant function in activating the Ptc1 signaling **pathway** during mammary gland development.
RE.CNT 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 8 OF 41 CAPLUS COPYRIGHT 2003 ACS
AN 2002:631673 CAPLUS
DN 137:349856
TI Patched acts catalytically to suppress the activity of Smoothened
AU Taipale, J.; Cooper, M. K.; Maiti, T.; Beachy, P. A.
CS Department of Molecular Biology and Genetics, Howard Hughes Medical Institute, Johns Hopkins University School of Medicine, Baltimore, MD, 21205, USA
SO Nature (London, United Kingdom) (2002), 418(6900), 892-896
CODEN: NATUAS; ISSN: 0028-0836
PB Nature Publishing Group
DT Journal
LA English
AB Mutations affecting the transmembrane proteins **Patched** (Ptc) or Smoothened (Smo) that trigger ligand-independent activity of the **Hedgehog** (Hh) signaling **pathway** are assocd. with human tumors such as basal cell carcinoma (BCC) and medulloblastoma. Despite extensive genetic studies demonstrating the importance of these receptor components in embryonic patterning and cancer, the mechanism by which Ptc regulates Smo is not understood. Here we report that Ptc and Smo are not significantly assocd. within Hh-responsive cells. Furthermore, we show that free Ptc (unbound by Hh) acts sub-stoichiometrically to suppress Smo activity and thus is crit. in specifying the level of **pathway** activity. **Patched** is a twelve-transmembrane protein with homol. to bacterial proton-driven transmembrane mol. transporters; we demonstrate that the function of Ptc is impaired by alterations of residues that are conserved in and required for function of these bacterial transporters. These results suggest that the Ptc tumor suppressor functions **normally** as a transmembrane mol. transporter, which acts indirectly to inhibit Smo activity, possibly through changes in distribution or concn. of a small mol.
RE.CNT 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 9 OF 41 CAPLUS COPYRIGHT 2003 ACS
AN 2002:613019 CAPLUS
DN 137:184414
TI Sonic hedgehog promotes cell cycle progression in activated peripheral CD4+ T lymphocytes
AU Lowrey, Jacqueline A.; Stewart, Gareth A.; Lindey, Susannah; Hoyne, Gerard F.; Dallman, Margaret J.; Howie, Sarah E. M.; Lamb, Jonathan R.
CS Immunobiology Group, Medical Research Council Center for Inflammation Research, Respiratory Medicine Unit, University of Edinburgh Medical School, Edinburgh, EH8 9AG, UK
SO Journal of Immunology (2002), 169(4), 1869-1875
CODEN: JOIMA3; ISSN: 0022-1767
PB American Association of Immunologists
DT Journal
LA English
AB Sonic **hedgehog** (Shh) signaling is important in the growth and differentiation of many cell types and recently has been reported to play a role in T cell development in the thymus. This prompted us to investigate whether or not Shh contributes to the clonal expansion of peripheral CD4+ T cells. In this study, we demonstrate that Shh and other components of the signaling **pathway patched,** smoothened, and Gli1 (glioma-assocd. oncogene) are expressed in peripheral CD4+ T cells. The addn. of the biol. active amino-terminal Shh peptide had no effect on resting CD4+ T cells, but significantly enhanced proliferation of anti-CD3/28 Ab-activated CD4+ T cells. This was not due to antiapoptotic effects, but by promoting entry of T cells into the S-G2 proliferative phase of the cell cycle. Neutralizing anti-Shh Ab reduced T cell proliferation by inhibiting cell transition into the S-G2 phase, suggesting that endogenously produced Shh plays a physiol. role in the clonal expansion of T cells. Furthermore, we have obsd. a significant up-regulation of Shh and Gli1 (glioma-assocd. oncogene) mRNA in activated CD4+ T cells with or without addn. of exogenous Shh, which corresponds with maximal CD4+ T cell proliferation, whereas bcl-2 was only upregulated in activated cells in the presence of Shh. Our findings suggest that endogenously produced Shh may play a role in sustaining **normal** CD4+ T cell proliferation and exogenously added Shh enhances this response.
RE.CNT 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 10 OF 41 CAPLUS COPYRIGHT 2003 ACS
AN 2002:612915 CAPLUS
DN 138:202199
TI In vivo enhanced expression of patched dampens the sonic hedgehog pathway
AU Bergstein, Ivan; Leopold, Philip L.; Sato, Noboru; Panteleyev, Andrei A.; Christiano, Angela M.; Crystal, Ronald G.
CS Division of Pulmonary and Critical Care Medicine, Division of Hematology-Oncology, Weill Medical College of Cornell University, New York, NY, 10021, USA
SO Molecular Therapy (2002), 6(2), 258-264
CODEN: MTOHCK; ISSN: 1525-0016
PB Elsevier Science
DT Journal
LA English
AB The sonic **hedgehog** (SHH)-**patched** (PTCH) **pathway** functions in **normal** embryonic development of the brain, musculoskeletal system, and hair follicles, and in **normal** post-natal control of hair follicles. Dysregulation of the **pathway** has been implicated in a variety of neoplasias, including those of skin and brain. Based on the knowledge that generalized, prolonged PTCH expression can inhibit the effects of SHH signaling, we tested the hypothesis that localized transient overexpression of PTCH would inhibit the phenotype of SHH-induced accelerated growth of hair follicles. Adenovirus (Ad)-mediated transient over-expression of Shh (AdShh) in telogen (8 wk) mouse skin induced anagen hair growth as demonstrated by histol. and gross appearance. Strikingly, local intradermal administration of a Ptch-expressing adenovirus (AdPtch), but not a Null control adenovirus (AdNull), 18 h before AdShh injection, significantly blocked this phenotype, with 100% of AdPtch + AdShh mice failing to advance to anagen compared with AdNull + AdShh mice and AdShh mice (30% and 45% failing to advance to anagen, resp.). Thus, PTCH expression mediated by gene transfer can modulate the SHH signaling **pathway** in the adult mammal and may serve as a starting point for therapies relevant to clin. conditions resulting from dysregulation of this **pathway** as well as for strategies to suppress **normal** SHH-dependent processes, such as hair growth.
RE.CNT 60 THERE ARE 60 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 11 OF 41 CAPLUS COPYRIGHT 2003 ACS
AN 2002:601056 CAPLUS
DN 137:335838
TI CUSP/p63 expression in basal cell carcinoma
AU Dellavalle, R. P.; Walsh, P.; Marchbank, A.; Grayson, T. E.; Su, L.-J.; Parker, E. R.; DeGregori, J.; Penheiter, K.; Aszterbaum, M.; Epstein, E. H., Jr.; Lee, L. A.
CS Department of Dermatology, University of Colorado School of Medicine, Denver, CO, USA
SO Experimental Dermatology (2002), 11(3), 203-208
CODEN: EXDEEY; ISSN: 0906-6705
PB Blackwell Munksgaard
DT Journal
LA English
AB Chronic ulcerative stomatitis protein (CUSP), the most abundant cutaneous isoform of p63, is a p53-related gene essential for epithelial development. CUSP lacks the N-terminal transactivation domain found on other p53 family members and has been shown to inhibit p53 function in vitro. In this study, biopsies of **normal** skin (21 of 21), benign neoplasms [seborrheic keratosis (3 of 3), acrochordon (2 of 3), and verruca plana (3 of 3)], and squamous cell carcinomas (SCC) (4 of 4) displayed strong nuclear CUSP immuno-reactivity in epidermal cells. In contrast few basal cell carcinomas (BCC) (7 of 27) and sebaceous nevi (1 of 2) displayed this pattern of CUSP immunoreactivity. Thus, biopsies of cutaneous conditions characterized by sonic **hedgehog** (SHH) **pathway** dysregulation were more than 86 times as likely to lack CUSP/p63 immunofluorescence as were other cutaneous samples. Adjacent **normal**-appearing skin from patients with basal cell nevus syndrome (BCNS) (2 of 3) also lacked CUSP immuno-staining. Lastly, a BCC arising in a **patched** heterozygous mouse also lacked CUSP immuno-staining. Because CUSP mRNA and protein were detected via Northern and Western anal. in BCC samples lacking CUSP immuno-staining, we sequenced the coding region of CUSP from two non-staining BCCs but found no mutations. Therefore, CUSP appears to be present, unmutated, and yet frequently undetectable by immunofluorescence in cutaneous lesions in both humans and mice that are assocd. with SHH **pathway** dysregulation (BCCs, BCNS, and nevus sebaceous).
RE.CNT 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 12 OF 41 CAPLUS COPYRIGHT 2003 ACS
AN 2002:370599 CAPLUS
DN 137:106725
TI A positive role for Patched-Smoothened signaling in promoting cell proliferation during normal head development in Drosophila
AU Shyamala, Baragur V.; Bhat, Krishna Moorthi
CS Department of Cell Biology, Emory University School of Medicine, Atlanta, GA, 30322, USA
SO Development (Cambridge, United Kingdom) (2002), 129(8), 1839-1847
CODEN: DEVPED; ISSN: 0950-1991
PB Company of Biologists Ltd.
DT Journal
LA English
AB The transmembrane receptor **Patched** (Ptc) regulates several developmental processes in both invertebrates and vertebrates. In vertebrates, **Patched** also acts as a tumor suppressor. The **Patched pathway normally** operates by neg. regulating Smoothened, a G-protein-coupled receptor; binding of **Hedgehog** ligand to **Patched** relieves this neg. interaction and allows signaling by Smoothened. The authors show that Ptc regulates Drosophila head development by promoting cell proliferation in the eye-antennal disk. During head morphogenesis, **Patched** pos. interacts with Smoothened, which leads to the activation of Activin type I receptor Baboon and stimulation of cell proliferation in the eye-antennal disk. Thus, loss of Ptc or Smoothened activity affects cell proliferation in the eye-antennal disk and results in adult head capsule defects. Similarly, reducing the dose of smoothened in a **patched** background enhances the head defects. Consistent with these results, gain-of-function **Hedgehog** interferes with the activation of Baboon by **Patched** and Smoothened, leading to a similar head capsule defect. Expression of an activated form of Baboon in the **patched** domain in a **patched** mutant background completely rescues the head defects. These results provide insight into head morphogenesis, a process the authors know very little about, and reveal an unexpected non-canonical pos. signaling **pathway** in which **Patched** and Smoothened function to promote cell proliferation as opposed to repressing it.
RE.CNT 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 13 OF 41 CAPLUS COPYRIGHT 2003 ACS
AN 2002:370479 CAPLUS
DN 137:107202
TI Developmentally-related candidate retinoic acid target genes regulated early during neuronal differentiation of human embryonal carcinoma
AU Freemantle, Sarah J.; Kerley, Joanna S.; Olsen, Shannon L.; Gross, Robert H.; Spinella, Michael J.
CS The Department of Pharmacology and Toxicology, Dartmouth Medical School, Hanover, NH, 03755, USA
SO Oncogene (2002), 21(18), 2880-2889
CODEN: ONCNES; ISSN: 0950-9232
PB Nature Publishing Group
DT Journal
LA English
AB Embryonal carcinoma is a model of embryonic development as well as tumor cell differentiation. In response to all-trans retinoic acid (RA), the human embryonal carcinoma (EC) cell line, NT2/D1, differentiates toward a neuronal lineage with assocd. loss of cell growth and tumorigenicity. Through the use of cDNA-based microarrays we sought to identify the early downstream targets of RA during differentiation commitment of NT2/D1 cells. A total of 57 genes were induced and 37 genes repressed by RA. RA regulated genes were restricted at 8 h with 27 genes induced and five repressed. The total no. of RA-responsive transcripts increased at 24 and 48 h and their pattern of expression was more sym. For a given time point less than 1% of the 9128 cDNAs on the expression array were regulated by RA. Many of these gene products are assocd. with developmental **pathways** including those of TGF-.beta. (Lefty A, NMA, follistatin), homeo domain (HoxD1, Meis2, Meis1, Gbx2), IGF (IGFBP3, IGFBP6, CTGF), Notch (manic fringe, ADAM11), **Hedgehog** (**patched**) and Wnt (Frat2, secreted frizzled-related protein 1) signaling. In addn. a large cassette of genes induced by RA at 24-48 h are assocd. with cell adhesion, cytoskeletal and matrix remodeling, growth suppression and intracellular signaling cascades. The majority of repressed genes are assocd. with protein/RNA processing, turnover or metab. The early induced genes identified may play a regulatory role in RA-mediated growth suppression and terminal differentiation and may have physiol. or pharmacol. importance during **normal** human development and retinoid-based cancer therapy or prevention.
RE.CNT 66 THERE ARE 66 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 14 OF 41 CAPLUS COPYRIGHT 2003 ACS
AN 2002:318099 CAPLUS
DN 137:182914
TI Indian Hedgehog as a Progesterone-Responsive Factor Mediating Epithelial-Mesenchymal Interactions in the Mouse Uterus
AU Matsumoto, Hiromichi; Zhao, Xuemei; Das, Sanjoy K.; Hogan, Brigid L. M.; Dey, Sudhansa K.
CS Department of Molecular, University of Kansas Medical Center, Kansas City, KS, 66160-7336, USA
SO Developmental Biology (Orlando, FL, United States) (2002), 245(2), 280-290
CODEN: DEBIAO; ISSN: 0012-1606
PB Elsevier Science
DT Journal
LA English
AB Genes encoding components of the **hedgehog** signaling **pathway** are dynamically expressed in the mouse uterus prepg. for implantation. Indian **hedgehog** (Ihh), **patched** (Ptc), and Gli3 are expressed at low levels in the endometrial epithelium on day 1 of pregnancy. Transcription of Ihh increases dramatically in the luminal epithelium and glands from day 3, reaching very high levels on day 4. Over the same period, Ptc, Gli1, Gli2, and noggin are strongly upregulated in the underlying mesenchymal stroma. Transcription of Ihh in ovariectomized mice is induced by progesterone but not by estrogen. Lower induction of Ihh, Ptc, and Hoxa10 is seen in response to progesterone in the uteri of Pgr-/- mutant mice lacking progesterone nuclear steroid receptor. This finding suggests that the hormone may regulate Ihh through both nuclear receptor-dependent and -independent **pathways**. We describe a method for culturing uterine explants in the absence of epithelium. Under these conditions, recombinant N-SHH protein promotes the proliferation of mesenchyme cells and the expression of noggin. We propose that IHH made by the epithelium **normally** functions as a paracrine growth factor for stromal cells during the early stages of pregnancy.
RE.CNT 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 15 OF 41 CAPLUS COPYRIGHT 2003 ACS
AN 2002:259980 CAPLUS
DN 137:261195
TI Mutations in PATCHED-1, the receptor for SONIC HEDGEHOG, are associated with holoprosencephaly
AU Ming, Jeffrey E.; Kaupas, Michelle E.; Roessler, Erich; Brunner, Han G.; Golabi, Mahin; Tekin, Mustafa; Stratton, Robert F.; Sujansky, Eva; Bale, Sherri J.; Muenke, Maximilian
CS Departments of Pediatrics and Genetics, Division of Human Genetics, University of Pennsylvania School of Medicine, Children's Hospital of Philadelphia, Philadelphia, PA, USA
SO Human Genetics (2002), 110(4), 297-301
CODEN: HUGEDQ; ISSN: 0340-6717
PB Springer-Verlag
DT Journal
LA English
AB Holoprosencephaly (HPE) is the most commonly occurring congenital structural forebrain anomaly in humans. HPE is assocd. with mental retardation and craniofacial malformations. The genetic causes of HPE have recently begun to be identified, and the authors have previously shown that HPE can be caused by haploinsufficiency for SONIC **HEDGEHOG** (SHH). The authors hypothesize that mutations in genes encoding other components of the SHH signaling **pathway** could also be assocd. with HPE. **PATCHED**-1 (PTCH), the receptor for SHH, **normally** acts to repress SHH signaling. This repression is relieved when SHH binds to PTCH. The authors analyzed PTCH as a candidate gene for HPE. Four different mutations in PTCH were detected in five unrelated affected individuals. The authors predict that by enhancing the repressive activity of PTCH on the SHH **pathway**, these mutations cause decreased SHH signaling, and HPE results. The mutations could affect the ability of PTCH to bind SHH or perturb the intracellular interactions of PTCH with other proteins involved in SHH signaling. These findings further demonstrate the genetic heterogeneity assocd. with HPE, as well as showing that mutations in different components of a single signaling **pathway** can result in the same clin. condition.
RE.CNT 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 16 OF 41 CAPLUS COPYRIGHT 2003 ACS
AN 2002:172887 CAPLUS
DN 137:107138
TI Expression of a sonic hedgehog signal transducer, hedgehog-interacting protein, by human basal cell carcinoma
AU Tojo, M.; Kiyosawa, H.; Iwatsuki, K.; Kaneko, F.
CS Departments of Dermatology, Fukushima Medical University School of Medicine, Fukushima, 960-1295, Japan
SO British Journal of Dermatology (2002), 146(1), 69-73
CODEN: BJDEAZ; ISSN: 0007-0963
PB Blackwell Science Ltd.
DT Journal
LA English
AB Aberrant activation of the **hedgehog pathway** was identified in various human tumors, including familial and sporadic basal cell carcinomas (BCCs). It was postulated that binding of sonic **hedgehog** protein (SHH) to its receptor, **patched** protein (PTC), releases the inhibitory effect of PTC against smoothened protein (SMO), another protein of the SHH signaling **pathway**. The pos. SMO signaling is not downregulated in BCCs because of the mutational inactivation of PTC. Recently, **hedgehog**-interacting protein (HIP) was found to bind to SHH directly and attenuate SHH signaling like PTC, while its expression was induced by SHH signals. To examine the expression patterns of HIP, SHH and PTC gene mRNA by human BCCs, in comparison with those by **normal** human skin and various skin tumors. We performed quant. reverse transcriptase-polymerase chain reaction analyses with a series of samples from BCCs, other skin tumors and **normal** skin. We found that the mRNA expression of both HIP and PTC genes was enhanced in all samples of BCCs, whereas none of the other skin tumors tested exhibited an increased level of such mRNAs as compared with **normal** skin. The transcription of the SHH gene, however, was at a baseline level in most BCCs. These results indicate that both HIP and PTC gene expression are specifically involved in the development of BCCs, and that the prodn. of HIP is linked with the expression of the PTC gene but not the SHH gene.
RE.CNT 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 17 OF 41 CAPLUS COPYRIGHT 2003 ACS
AN 2001:886320 CAPLUS
DN 137:58414
TI Genetic evidence that Sil is required for the sonic hedgehog response pathway
AU Izraeli, Shai; Lowe, Linda A.; Bertness, Virginia L.; Campaner, Stefano; Hahn, Heidi; Kirsch, Ilan R.; Kuehn, Michael R.
CS Genetics Branch, Center for Cancer Research, National Cancer Institute, NIH, Bethesda, MD, 20892-1360, USA
SO Genesis (New York, NY, United States) (2001), 31(2), 72-77
CODEN: GNESFY; ISSN: 1526-954X
PB Wiley-Liss, Inc.
DT Journal
LA English
AB The Sil gene encodes a cytosolic protein required for mouse embryonic midline and left/right axial development. Based on the phenotype of Sil mutant embryos, we hypothesized that Sil may be required for the activity of Sonic **Hedgehog** (Shh), a secreted signaling mol. also critically important for the development of the embryonic axes and found mutated in multiple types of cancer. Here we tested the genetic interaction between Sil and the Shh **pathway** by generating and analyzing embryos carrying mutations in both Sil and **Patched** (Ptch), a Shh receptor that **normally** inhibits the signaling **pathway** in the absence of ligand and when mutated leads to constitutive activation of the **pathway**. We find that Sil-/- Ptch-/- embryos do not activate the Shh **pathway** and instead have a phenotype indistinguishable from Sil-/- embryos, in which there is a loss of activity of Shh. These results provide genetic evidence that Sil is an essential component of the Shh response, acting downstream to Ptch.
RE.CNT 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 18 OF 41 CAPLUS COPYRIGHT 2003 ACS
AN 2001:560211 CAPLUS
DN 135:270811
TI The developmental biology of brain tumors
AU Wechsler-Reya, Robert; Scott, Matthew P.
CS Departments of Developmental Biology and Genetics and Howard Hughes Medical Institute, Stanford University School of Medicine, Stanford, CA, 94305-5329, USA
SO Annual Review of Neuroscience (2001), 24, 385-428
CODEN: ARNSD5; ISSN: 0147-006X
PB Annual Reviews Inc.
DT Journal; General Review
LA English
AB A review with many refs. Tumors of the central nervous system (CNS) can be devastating because they often affect children, are difficult to treat, and frequently cause mental impairment or death. New insights into the causes and potential treatment of CNS tumors have come from discovering connections with genes that control cell growth, differentiation, and death during **normal** development. Links between tumorigenesis and **normal** development are illustrated by three common CNS tumors: retinoblastoma, glioblastoma, and medulloblastoma. For example, the retinoblastoma (Rb) tumor suppressor protein is crucial for control of **normal** neuronal differentiation and apoptosis. Excessive activity of the epidermal growth factor receptor and loss of the phosphatase PTEN are assocd. with glioblastoma, and both genes are required for **normal** growth and development. The membrane protein **Patched1** (Ptc1), which controls cell fate in many tissues, regulates cell growth in the cerebellum, and reduced Ptc1 function contributes to medulloblastoma. Just as elucidating the mechanisms that control **normal** development can lead to the identification of new cancer-related genes and signaling **pathways**, studies of tumor biol. can increase our understanding of **normal** development. Learning that Ptc1 is a medulloblastoma tumor suppressor led directly to the identification of the Ptc1 ligand, Sonic **hedgehog**, as a powerful mitogen for cerebellar granule cell precursors. Much remains to be learned about the genetic events that lead to brain tumors and how each event regulates cell cycle progression, apoptosis, and differentiation. The prospects for beneficial work at the boundary between oncol. and developmental biol. are great.
RE.CNT 324 THERE ARE 324 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 19 OF 41 CAPLUS COPYRIGHT 2003 ACS
AN 2001:285828 CAPLUS
DN 135:270698
TI The hedgehog signaling pathway and cancer
AU Saldanha, Gerald
CS Breast Cancer Research Unit, Glenfield Hospital, Leicester, LE3 9QP, UK
SO Journal of Pathology (2001), 193(4), 427-432
CODEN: JPTLAS; ISSN: 0022-3417
PB John Wiley & Sons Ltd.
DT Journal; General Review
LA English
AB A review with 90 refs. The **Hedgehog** signaling **pathway** is important in embryol. development and is highly conserved through evolution. Recently **Patched**, a member of the **pathway**, was found to be important in Gorlin's syndrome. Inherited **Patched** gene mutations underlie the syndrome, in which a key feature is multiple basal cell carcinomas (BCCs). The gene is also mutated in sporadic BCCs as well as in sporadic occurrences of other tumors seen in Gorlin's syndrome. The precise mechanism whereby **Patched** gene mutation leads to tumor development is not known, but BCC is characterized by relentless local invasion and only rarely metastasizes. This suggests that abnormalities of the **Hedgehog pathway** account for these features. This proposal is discussed in the context of what is already known about the **normal** function of the **Hedgehog pathway** and its deregulation in cancer.
RE.CNT 90 THERE ARE 90 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 20 OF 41 CAPLUS COPYRIGHT 2003 ACS
AN 2000:908355 CAPLUS
DN 134:234587
TI Downregulation of Hedgehog signaling is required for organogenesis of the small intestine in Xenopus
AU Zhang, Jian; Rosenthal, Arnon; de Sauvage, Frederic J.; Shivdasani, Ramesh A.
CS Department of Molecular Oncology, Genentech, Inc., South San Francisco, CA, 94080, USA
SO Developmental Biology (Orlando, FL, United States) (2001), 229(1), 188-202
CODEN: DEBIAO; ISSN: 0012-1606
PB Academic Press
DT Journal
LA English
AB **Hedgehog** ligands interact with receptor complexes contg. **Patched** (PTC) and Smoothened (SMO) proteins to regulate many aspects of development. The mutation W535L (SmoM2) in human Smo is assocd. with basal cell skin cancers, causes constitutive, ligand-independent signaling through the **Hedgehog pathway**, and provides a powerful means to test effects of unregulated **Hedgehog** signaling. Expression of SmoM2 in Xenopus embryos leads to developmental anomalies that are consistent with known requirements for regulated **Hedgehog** signaling in the eye and pancreas. Addnl., it results in failure of midgut epithelial cytodifferentiation and of the intestine to lengthen and coil. The midgut mesenchyme shows increased cell nos. and attenuated expression of the differentiation marker smooth muscle actin. With the exception of the pancreas, differentiation of foregut and hindgut derivs. is unaffected. The intestinal epithelial abnormalities are reproduced in embryos or organ explants treated directly with active recombinant **hedgehog** protein. Ptc mRNA, a principal target of **Hedgehog** signaling, is maximally expressed at stages corresponding to the onset of the intestinal defects. In advanced embryos expressing SmoM2, Ptc expression is remarkably confined to the intestinal wall. Considered together, these findings suggest that the splanchnic mesoderm responds to endodermal **Hedgehog** signals by inhibiting the transition of midgut endoderm into intestinal epithelium and that attenuation of this feedback is required for **normal** development of the vertebrate intestine.

RE.CNT 69 THERE ARE 69 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 21 OF 41 CAPLUS COPYRIGHT 2003 ACS
AN 2000:745456 CAPLUS
DN 134:98467
TI Erythroid Differentiation in Vitro Is Blocked by Cyclopamine, an Inhibitor of Hedgehog Signaling
AU Detmer, Kristina; Walker, Anna N.; Jenkins, Tracie M.; Steele, Timothy A.; Dannawi, Hassan; Lichtman, Marshall
CS Division of Basic Medical Sciences, Mercer University School of Medicine, Macon, GA, 31207, USA
SO Blood Cells, Molecules & Diseases (2000), 26(4), 360-372
CODEN: BCMDFX; ISSN: 1079-9796
PB Academic Press
DT Journal
LA English
AB Adult hematopoietic differentiation is a developmental process that employs many of the same mol. mechanisms as embryogenesis. To explore the possibility that **hedgehog** signaling is involved in the control of hematopoietic differentiation, we screened a panel of human leukemia cell lines for the expression of **Patched1** and Smoothened, the receptor and coreceptor for **hedgehog** ligands. Expression was found in multiple cell lines, and **Patched1** expression was detected in **normal** marrow. Induction of myeloid differentiation in cell lines downregulated expression of both genes. When **normal** marrow mononuclear cells were grown in semisolid medium in the presence of 10 .mu.M cyclopamine, development of colonies of granulocytic/monocytic lineage was unaffected in terms of both no. and morphol. The no. of erythroid colonies, however, was significantly reduced ($P < 0.01$). Furthermore, hemoglobinization was substantially delayed relative to controls in those erythroid colonies that did form. Incubation of hematopoietic progenitors with Shh-N and GM-CSF resulted in increased granulocyte/monocyte colonies ($P < 0.01$); the increase was blocked by cyclopamine. Incubation of hematopoietic progenitors with Shh-N and stem cell factor resulted in larger erythroid colonies. These results suggest that elements of the **hedgehog** signaling **pathway** are involved in the control of hematopoietic differentiation. (c) 2000 The Blood Cells Foundation, La Jolla, CA, USA.
RE.CNT 56 THERE ARE 56 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 22 OF 41 CAPLUS COPYRIGHT 2003 ACS
AN 2000:651546 CAPLUS
DN 133:360983
TI Posttranscriptional regulation of smoothened is part of a self-correcting mechanism in the Hedgehog signaling system
AU Alcedo, Joy; Zou, Yu; Noll, Markus
CS Institute for Molecular Biology, University of Zurich, Zurich, CH-8057, Switz.
SO Molecular Cell (2000), 6(2), 457-465
CODEN: MOCEFL; ISSN: 1097-2765
PB Cell Press
DT Journal
LA English
AB **Hedgehog** signaling, mediated through its **Patched** -Smoothened receptor complex, is essential for pattern formation in animal development. Activating mutations within Smoothened have been assocd. with basal cell carcinoma, suggesting that smoothened is a protooncogene. Thus, regulation of Smoothened levels might be crit. for **normal** development. We show that Smoothened protein levels in Drosophila embryos are regulated posttranscriptionally by a mechanism dependent on **Hedgehog** signaling but not on its nuclear effector Cubitus interruptus. **Hedgehog** signaling upregulates Smoothened levels, which are otherwise downregulated by **Patched**. Demonstrating properties of a self-correcting system, the **Hedgehog** signaling **pathway** adjusts the concns. of Smoothened and **Patched** to each other and to that of the **Hedgehog** signal, which ensures that activation of **Hedgehog** target genes by Smoothened signaling becomes strictly dependent on **Hedgehog**.
RE.CNT 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 23 OF 41 CAPLUS COPYRIGHT 2003 ACS
AN 2000:493313 CAPLUS
DN 133:99549
TI Regulation of the hedgehog pathway and smoothened gain-of-function by gene patched agonists
IN Dudek, Henryk; Ji, Benxiu
PA Ontogeny, Inc., USA
SO PCT Int. Appl., 114 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2000041545	A2	20000720	WO 2000-US873	20000113
	WO 2000041545	A3	20000928		
	W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	US 6291516	B1	20010918	US 1999-417564	19991014
	EP 1143961	A2	20011017	EP 2000-906910	20000113
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
	US 2001034337	A1	20011025	US 2001-867311	20010529
PRAI	US 1999-115642P	P	19990113		
	US 1999-119594P	P	19990210		
	US 1999-142124P	P	19990702		
	US 1999-417564	A	19991014		
	WO 2000-US873	W	20000113		

OS MARPAT 133:99549
AB The present invention makes available methods and reagents for inhibiting aberrant growth states resulting from **hedgehog** gain-of-function, **patched** (ptc) loss-of-function or smoothened gain-of-function comprising contacting a cell with a compd., such as a polypeptide or small mol. in an amt. sufficient to control the aberrant growth state, e.g., to agonize a **normal** ptc **pathway** or antagonize smoothened or **hedgehog** activity. The present invention further makes available methods and reagents for ameliorating the consequences of **hedgehog** loss-of-function, ptc gain-of-function, or smoothened loss-of-function comprising contacting a cell with a compd., such as a polypeptide or small mol., in an amt. sufficient for amelioration. In certain embodiments, the subject compds., e.g., a cAMP analog, adenylate cyclase agonist, or cAMP phosphodiesterase inhibitor, regulate cAMP levels, which in turn modulates activity of the **hedgehog pathway**. Thus, compds. such as jervine, cyclopamine, and forskolin analogs are also effective in inhibition of medulloblastoma.

L5 ANSWER 24 OF 41 CAPLUS COPYRIGHT 2003 ACS
AN 2000:282741 CAPLUS
DN 133:41366
TI The normal patched allele is expressed in medulloblastomas from mice with heterozygous germ-line mutation of patched
AU Wetmore, Cynthia; Eberhart, Derek E.; Curran, Tom
CS Departments of Developmental Neurobiology and Hematology/Oncology, St. Jude Children's Research Hospital, Memphis, TN, 38105, USA
SO Cancer Research (2000), 60(8), 2239-2246
CODEN: CNREA8; ISSN: 0008-5472
PB American Association for Cancer Research
DT Journal
LA English
AB Defects in a developmental signaling **pathway** involving mammalian homologs of the Drosophila segment polarity gene, **patched** (ptc) and its ligand, sonic **hedgehog** (shh), contribute to tumor formation in several tissues. Recently, a subset of medulloblastoma, the most common malignant brain tumor in children, was found to contain somatic mutations in the human ptc gene. In addn., basal cell nevus syndrome (BCNS), or Gorlin syndrome, which is characterized by developmental anomalies and a predisposition to skin and nervous system malignancies, is assocd. with germ-line mutation of ptc. Targeted disruption of both alleles of ptc in mice results in embryonic lethality. However, ptc+/- mice survive and develop spontaneous cerebellar brain tumors, suggesting that ptc may function as a tumor suppressor gene. Therefore, we investigated ptc+/- mice as a model for human medulloblastoma. We report that 14% of ptc+/- mice develop central nervous system tumors in the posterior fossa by 10 mo of age, with peak tumor incidence occurring between 16 and 24 wk of age. The tumors exhibited several characteristics of human medulloblastoma, including expression of intermediate filament proteins specific for neurons and glia. Full-length ptc mRNA was present in all tumors analyzed, indicating that there was no loss of heterozygosity at the ptc locus. Nucleotide sequence of ptc mRNA from four tumors failed to identify any mutations. However, a comparison of the **normal** ptc sequence from C57BL/6 and 129Sv mice did reveal several polymorphisms. High levels of gli1 mRNA and protein were detected in the tumors, suggesting that the shh/ptc **pathway** was activated despite the persistence of ptc expression. These data indicate that haploinsufficiency of ptc is sufficient to promote oncogenesis in the central nervous system.
RE.CNT 49 THERE ARE 49 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 25 OF 41 CAPLUS COPYRIGHT 2003 ACS
AN 2000:224643 CAPLUS
DN 133:13078
TI Targeted Misexpression of Constitutively Active BMP Receptor-IB Causes Bifurcation, Duplication, and Posterior Transformation of Digit in Mouse Limb
AU Zhang, Zunyi; Yu, Xueyan; Zhang, Yanding; Geronimo, Benedicto; Lovlie, Arne; Fromm, Sigurd H.; Chen, YiPing
CS Department of Oral Biology, University of Oslo, Oslo, 0316, Norway
SO Developmental Biology (2000), 220(2), 154-167
CODEN: DEBIAO; ISSN: 0012-1606
PB Academic Press
DT Journal
LA English
AB Members of bone morphogenetic proteins (BMPs) play important roles in many aspects of vertebrate embryogenesis. In developing limbs, BMPs have been implicated in control of anterior-posterior patterning, outgrowth, chondrogenesis, and apoptosis. These diverse roles of BMPs in limb development are apparently mediated by different BMP receptors (BMPR). To identify the developmental processes in mouse limb possibly contributed by BMP receptor-IB (BMPR-IB), we generated transgenic mice misexpressing a constitutively active Bmpr-IB (caBmpr-IB). The transgene driven by the mouse Hoxb-6 promoter was ectopically expressed in the posterior mesenchyme of the forelimb bud, the lateral plate mesoderm, and the whole mesenchyme of the hindlimb bud. While the forelimbs appeared **normal**, the transgenic hindlimbs exhibited several phenotypes, including bifurcation, preaxial polydactyly, and posterior transformation of the anterior digit. However, the size of bones in the transgenic limbs seemed unaltered. Defects in sternum and ribs were also found. The bifurcation in the transgenic hindlimb occurred early in the limb development (E10.5) and was assocd. with extensive cell death in the mesenchyme and occasionally in the apical ectodermal ridge (AER). Sonic **hedgehog** (Shh) and **Patched** (Ptc) expression appeared unaffected in the transgenic limb buds, suggesting that the BMPR-IB mediated signaling **pathway** is downstream from Shh. However, ectopic Fgf4 expression was found in the anterior AER, which may account for the duplication of the anterior digit. An ectopic expression of Gremlin found in the transgenic limb bud would be responsible for the ectopic Fgf4 expression. The observations that Hoxd-12 and Hoxd-13 expression patterns were extended anteriorly provide a mol. basis for the posterior transformation of the anterior digit. Together these results suggest that BMPR-IB is the endogenous receptor to mediate the role of BMPs in anterior-posterior patterning and apoptosis in mouse developing limb. In addn., BMPR-IB may represent a crit. component in the Shh/FGF4 feedback loop by regulating Gremlin expression. (c) 2000 Academic Press.
RE.CNT 81 THERE ARE 81 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 26 OF 41 CAPLUS COPYRIGHT 2003 ACS
AN 2000:65569 CAPLUS
DN 133:14991
TI The SREBP pathway. Controlling cholesterol metabolism by proteolysis of a membrane-bound transcription factor
AU Sakai, Juro
CS Sch. Med., Tohoku Univ., Miyagi, 989-6435, Japan
SO Molecular Medicine (Tokyo) (1999), Volume Date 2000, 37(1), 46-57
CODEN: MOLMEL; ISSN: 0918-6557
PB Nakayama Shoten
DT Journal; General Review
LA Japanese
AB A review with 34 refs. Sterol regulatory element binding protein (SREBP) binds sterol regulatory element 1 (SRE-1). SRE-1 is a common element in **pathways** of low d. lipoprotein (LDL)-cholesterol uptake and de novo synthesis. SREBP-1a, SREBP-1c and SREBP-2 are cloned from human c-DNA library, and SREBP-1c is the rat counterpart gene of ADD1 (adipocyte detn.- and differentiation-dependent factor 1). SREBP consists of 3 main domains including basic helix-loop-helix leucine zipper structure, and activated by two-step processing in the sterol response. Site 1 processing of SREBP is strictly regulated by sterol deficiency, and the site 2 processing only occurs after site 1 processing. SREBP cleavage activating protein (SCAP) regulates site 1 processing, and a mutation of SCAP makes the processing free of sterol control found in 25RA cells. SCAP possesses homologous domain to **patched** that uses **hedgehog** as a ligand, and NPC1 relating Nieman-Pick disease. Cholesterol auxotroph cells of M19 lacks site 2 protease, which is a hydrophobic membrane protein. Site 1 protease is in subtilisin-like serine protease family. Forced expression of SREBP in transgenic mice activate not only cholesterol biosynthetic **pathway** but all **pathways** of lipid biosynthesis. Difference in isoforms of SREBP is discussed. Adipose-tissue specific expression of SREBP-1c/ADD1 in a transgenic mouse shows a phenotype of human congenital lipodystrophy. Supplement of leptin to the mouse **normalizes** fatty liver, insulin resistance and hyperglycemia.

L5 ANSWER 27 OF 41 CAPLUS COPYRIGHT 2003 ACS
AN 2000:27068 CAPLUS
DN 132:163752
TI Dispatched, a novel sterol-sensing domain protein dedicated to the release of cholesterol-modified Hedgehog from signaling cells
AU Burke, Richard; Nellen, Denise; Bellotto, Manolo; Hafen, Ernst; Senti, Kirsten-Andre; Dickson, Barry J.; Basler, Konrad
CS Institut fur Molekularbiologie Universitat Zurich, Zurich, CH-8057, Switz.
SO Cell (Cambridge, Massachusetts) (1999), 99(7), 803-815
CODEN: CELLB5; ISSN: 0092-8674
PB Cell Press
DT Journal
LA English
AB Members of the **Hedgehog** (Hh) family of secreted signaling proteins function as potent short-range organizers in animal development. Their range of action is limited by a C-terminal cholesterol tether and the upregulation of **Patched** (Ptc) receptor levels. Here we identify a novel segment-polarity gene in Drosophila, dispatched (disp), and demonstrate that its product is required in sending cells for **normal** Hh function. In the absence of Disp, cholesterol-modified but not cholesterol-free Hh is retained in these cells, indicating that Disp functions to release cholesterol-anchored Hh. Despite their opposite roles, Disp and Ptc share structural homol. in the form of a sterol-sensing domain, suggesting that release and sequestration of cholesterol-modified Hh may be based on related mol. **pathways.**
RE.CNT 54 THERE ARE 54 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 28 OF 41 CAPLUS COPYRIGHT 2003 ACS
AN 1999:644628 CAPLUS
DN 131:335035
TI Induction of the hair growth phase in postnatal mice by localized transient expression of sonic hedgehog
AU Sato, Noboru; Leopold, Philip L.; Crystal, Ronald G.
CS Division of Pulmonary and Critical Care Medicine, Weill Medical College of Cornell University-New York Presbyterian Hospital, New York, NY, 10021, USA
SO Journal of Clinical Investigation (1999), 104(7), 855-864
CODEN: JCINAO; ISSN: 0021-9738
PB American Society for Clinical Investigation
DT Journal
LA English
AB Hair follicles form in prenatal skin and mature in the postnatal period, establishing a growth cycle in 3 phases: telogen (resting), anagen (growth), and catagen (regression). Based on the knowledge that Sonic **hedgehog** (Shh) expression is necessary for the embryonic development of hair follicles, and that anagen in the postnatal cycling follicle has morphol. similarities to the epithelial invagination process in embryonic skin, we hypothesized that localized, but transient, enhanced expression of the Shh gene in postnatal skin would accelerate initiation of anagen in the hair follicle cycle, with concomitant accelerated hair growth. To assess this concept, an E1- adenovirus vector, AdShh, was used to transfer the murine Shh cDNA to skin of postnatal day 19 C57BL/6 mice. The treated skin showed increased mRNA expression of Shh, **Patched** (the Shh receptor), and Gli1 (a transcription factor in the Shh **pathway**). In mice receiving AdShh, but not in controls, acceleration into anagen was evident, since hair follicle size and melanogenesis increased and the hair-specific keratin ghHb-1 and the melanin synthesis-related tyrosinase mRNAs accumulated. Finally, C57BL/6 mice showed marked acceleration of the onset of new hair growth in the region of AdShh administration to skin 2 wk after treatment, but not in control vector-treated or untreated areas. After 6 mo, AdShh-treated skin showed **normal** hair and **normal** skin morphol. Together, these observations are consistent with the concept that upregulation of Shh activity in postnatal skin functions as a biol. switch that induces resting hair follicles to enter anagen with consequent hair growth.
RE.CNT 53 THERE ARE 53 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 29 OF 41 CAPLUS COPYRIGHT 2003 ACS
AN 1999:425795 CAPLUS
DN 131:69298
TI Characterization of a human homolog of the Drosophila melanogaster Su(fu) gene and its involvement in PTC-GLI signaling
IN Toftgard, Rune; Zaphiropoulos, Peter G.; Kogerman, Priit; Grimm, Thomas
PA Karolinska Innovations AB, Swed.
SO PCT Int. Appl., 82 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9932517	A1	19990701	WO 1998-SE2383	19981218
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	AU 9919917	A1	19990712	AU 1999-19917	19981218
	EP 1037920	A1	20000927	EP 1998-964640	19981218
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
	US 6448020	B1	20020910	US 2000-581831	20000821
PRAI	SE 1997-4788	A	19971219		
	SE 1998-2293	A	19980626		
	WO 1998-SE2383	W	19981218		

AB The invention provides human and mouse homologs of the Drosophila Su(fu) (suppressor of fused) gene, which is involved in the transduction of signals elicited by the interaction between the **patched** receptor (PTC) and any one of the **hedgehog** ligands (the HH-PTC **pathway**). The protein sequence for human SUFUH demonstrates 40% identity and 61% similarity to the Drosophila melanogaster sequence, and the human and mouse genes show 98% identity. Human Su(fu) was mapped to chromosome 10q24 at a region frequently lost in several tumor types, making it a candidate for a tumor suppressor gene. The human gene also maps in a region assocd. with Split hand/Split foot Malformation Type 3 (SHFM3), and based on its involvement in a signaling **pathway** known to regulate limb development and its demonstrated expression during mouse limb development, Su(fu) is a strong candidate for the SHFM3 gene. Addnl., given its pattern of expression during embryogenesis and strong homol. to the Drosophila homolog, the involvement of human SUFUH in PTC-GLI signaling was tested. Results indicated that GLI-1 and SUFUH function very closely in the signal transduction **pathway** and raised the possibility that they might assoc. phys. or be in the same macromol. complex, as is reported for the Drosophila counterpart. Thus, the invention provides information important for the basic understanding of a signaling **pathway** that is central to **normal** development and is often disrupted in disease. The mols. according to the present invention are useful in diagnostic and therapeutic methods relating to conditions assocd. with defects in said **pathway**, esp. certain malformations and cancer. DNA and protein sequences for the human homolog are claimed, but they are not provided in the document.

RE.CNT 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 30 OF 41 CAPLUS COPYRIGHT 2003 ACS
AN 1999:411872 CAPLUS
DN 131:155942
TI Expression of ptc and gli genes in talpid3 suggests bifurcation in Shh pathway
AU Lewis, K. E.; Drossopoulou, G.; Paton, I. R.; Morrice, D. R.; Robertson, K. E.; Burt, D. W.; Ingham, P. W.; Tickle, C.
CS Developmental Genetics Programme, Krebs Institute, University of Sheffield, Sheffield, S10 2TN, UK
SO Development (Cambridge, United Kingdom) (1999), 126(11), 2397-2407
CODEN: DEVPED; ISSN: 0950-1991
PB Company of Biologists Ltd.
DT Journal
LA English
AB Talpid3 is an embryonic-lethal chicken mutation in a molecularly un-characterized autosomal gene. The recessive, pleiotropic phenotype includes polydactylous limbs with morphol. similar digits. Previous anal. established that hox-D and bmp genes, that are **normally** expressed posteriorly in the limb bud in response to a localized, posterior source of Sonic **Hedgehog** (Shh) are expressed sym. across the entire anteroposterior axis in talpid3 limb buds. In contrast, Shh expression itself is unaffected. Here we examine expression of **patched** (ptc), which encodes a component of the Shh receptor, and is probably itself a direct target of Shh signaling, to establish whether talpid3 acts in the Shh **pathway**. We find that ptc expression is significantly reduced in talpid3 embryos. We also demonstrate that talpid3 function is not required for Shh signal prodn. but is required for **normal** response to Shh signals, implicating talpid3 in transduction of Shh signals in responding cells. Our anal. of expression of putative components of the Shh **pathway**, gli1, gli3 and coupTFII shows that genes regulated by Shh are either ectopically expressed or no longer responsive to Shh signals in talpid3 limbs, suggesting possible bifurcation in the Shh **pathway**. We also describe genetic mapping of gli1, ptc, shh and smoothened in chickens and confirm by co-segregation anal. that none of these genes correspond to talpid3.
RE.CNT 73 THERE ARE 73 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 31 OF 41 CAPLUS COPYRIGHT 2003 ACS
AN 1999:211424 CAPLUS
DN 131:42837
TI Role of PTCH in cancer and development
AU Levanat, Sonja; Pavelic, Bozidar; Crnic, Ivana; Situm, Mirna; Manojlovic, Spomenka; Mubrin-Koncar, Mirjana; Basta-Juzbasic, Aleksandra
CS Division of Molecular Medicine, Ruder Boskovic Institute, Zagreb, 10000, Croatia
SO Periodicum Biologorum (1998), 100(3), 319-324
CODEN: PDBIAD; ISSN: 0031-5362
PB Hrvatsko Prirodoslovno Drustvo
DT Journal
LA English
AB Studies of mol. basis of hereditary syndromes that involve both cancer predisposition and birth defects may help understand the relation between neoplasia and development. The PTCH gene, a human homolog of the Drosophila segment polarity gene **patched**, is the gene responsible for Nevoid Basal Cell Carcinoma Syndrome (NBCCS) or Gorlin syndrome, and it is a tumor suppressor as well, at least for basocellular carcinomas of the skin (BCCs). Gorlin syndrome patients develop severe tumors (BCCs in particular) and multiple developmental defects, among which keratocysts of the jaws are most often. DNA from patients' peripheral blood leukocytes and matched tumor tissue were used in LOH (Loss of heterozygosity) studies, with polymorphic markers (D9S196, D9S287, D9S180, D9S127) and PTCH primers (exons 3, 6, 8, 13, 15, 16) in SSCP (single strand conformational polymorphism) studies. The authors examd. a series of chromosome 9q polymorphisms in tumorous (BCCs and ovarian fibroma) and non-tumorous (jaw cyst) samples from both Gorlin syndrome patients and sporadic cases and detected loss of heterozygosity (LOH) in PTCH region. In Gorlin syndrome cases the authors found that the cyst lining of jaws lost the **normal** copy of the PTCH region while retaining the mutant copy. The authors also found LOH in some sporadic jaw cysts. While it is generally recognized for keratocysts, the recent LOH findings seem to indicate that PTCH inactivation might also be responsible for follicular cysts. The authors searched for LOH in jaw cysts not only to test the hypothesis that anomalies in Gorlin syndrome might arise through a two-hit mechanism, but also to examine possible involvement of PTCH in formation of various jaw cysts unrelated to Gorlin syndrome. More generally, the authors looked for indications of PTCH role in manifestations which were not typical for NBCCS to contribute to delineation of the **hedgehog/patched pathway**.
RE.CNT 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 32 OF 41 CAPLUS COPYRIGHT 2003 ACS
AN 1998:345290 CAPLUS
DN 129:105064
TI Expression of wingless in the drosophila embryo: a conserved cis-acting element lacking conserved ci-binding sites is required for patched-mediated repression
AU Lessing, Derek; Nusset, Roel
CS Howard Hughes Medical Institute, Department of Developmental Biology, Beckman Center, Stanford University, Medical Center, Stanford, CA, 94305, USA
SO Development (Cambridge, United Kingdom) (1998), 125(8), 1469-1476
CODEN: DEVPED; ISSN: 0950-1991
PB Company of Biologists Ltd.
DT Journal
LA English
AB Patterning of the Drosophila embryo depends on the accurate expression of wingless (wg). which encodes a secreted signal required for segmentation and many other processes. Early expression of wg is regulated by the nuclear proteins of the gap and pair-rule gene classes but, after gastrulation. wg transcription is also dependent on cell-cell communication. Signaling to the Wg-producing cells is mediated by the secreted protein, **Hedgehog** (Hh), and by Cubitus interruptus (Ci), a transcriptional effector of the Hh signal transduction **pathway**. The transmembrane protein **Patched** (Ptc) acts as a neg. regulator of wg expression; ptc- embryos have ectopic wg expression. According to the current models, Ptc is a receptor for Hh. The default activity of Ptc is to inhibit Ci function; when Ptc binds Hh, this inhibition is released and Ci can control wg transcription. The authors have investigated cis-acting sequences that regulate wg during the time that wg expression depends on Hh signaling. The authors show that approx. 4.5 kb immediately upstream of the wg transcription unit can direct expression of the reporter gene lacZ in domains similar to the **normal** wg pattern in the embryonic ectoderm. Expression of this reporter construct expands in ptc mutants and responds to hh activity. Within this 4.5 kb, a 150 bp element, highly conserved between D. melanogaster and Drosophila virilis, is required to spatially restrict wg transcription. Activity of this element depends on ptc, but it contains no consensus Ci-binding sites. The discovery of an element that is likely to bind a transcriptional repressor was unexpected, since the prevailing model suggests that wg expression is principally controlled by Hh signaling acting through the Ci activator. We show that wg regulatory DNA can drive lacZ in a proper wg-like pattern without any conserved Ci-binding sites and suggest that Ci can not be the sole endpoint of the Hh **pathway**.
RE.CNT 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 33 OF 41 CAPLUS COPYRIGHT 2003 ACS
AN 1998:64692 CAPLUS
DN 128:152653
TI Expression of human GLI in mice results in failure to thrive, early death, and patchy Hirschsprung-like gastrointestinal dilatation
AU Yang, Jian Tao; Liu, Cheng Zheng; Villavicencio, Elisabeth H.; Yoon, Joon Won; Walterhouse, David; Iannaccone, Philip M.
CS Department of Pediatrics and Children's Memorial Institute for Education and Research, Northwestern University Medical School, Chicago, IL, 60614, USA
SO Molecular Medicine (New York) (1997), 3(12), 826-835
CODEN: MOMEF3; ISSN: 1076-1551
PB Springer-Verlag New York Inc.
DT Journal
LA English
AB GLI is an oncodevelopmental gene in the vertebrate **hedgehog/patched** signaling **pathway** that is spatiotemporally regulated during development and is amplified in a subset of human cancers. GLI is the prototype for the Gli-Kruppel family of transcription factors, which includes the Drosophila segment polarity gene ci, the C. elegans sex-detg. gene tra-1, and human and mouse GLI3, all of which contain a conserved domain of five C2-H2 zinc fingers. GLI3 mutations have been implicated in the mouse mutant extra toes, as well as in human Greig cephalopolydactaly syndrome and the autosomal dominant form of Pallister-Hall syndrome. As such, GLI and the vertebrate **hedgehog/patched** signaling **pathway** appear to play important roles in both **normal** development and neoplasia. Since it is not known whether aberrant GLI expression is similarly linked to developmental disorders, we developed gain-of-function transgenic mice which express human GLI ectopically. Affected transgenic mice exhibit a phenotype of failure to thrive, early death, and Hirschsprung-like patches of gastrointestinal dilatation. The colons of affected mice have greatly attenuated smooth muscle layers and abnormal overlying epithelium. The d. of myenteric plexuses is reduced in the colonic walls. The severity of the phenotype is related to the level of transgene expression. The transgenic mouse model supports a role for GLI in gastrointestinal development. As part of the vertebrate **hedgehog/patched** signaling **pathway**, GLI is essential to mesoderm and CNS ectoderm development and transgenic GLI expression affects neuronal, muscular, and epithelial cell differentiation in the gut. Expression of human GLI in mice results in impairment of enteric neuronal development and a Hirschsprung-like phenotype.

L5 ANSWER 34 OF 41 CAPLUS COPYRIGHT 2003 ACS
AN 1997:748329 CAPLUS
DN 128:137135
TI Hedgehog signaling regulates transcription through Gli/Ci binding sites in the wingless enhancer
AU Von Ohlen, Tonia; Hooper, Joan E.
CS CO, Department of Cellular and Structural Biology, University of Colorado Health Sciences Center, Denver, 80262, USA
SO Mechanisms of Development (1997), 68(1,2), 149-156
CODEN: MEDVE6; ISSN: 0925-4773
PB Elsevier Science Ireland Ltd.
DT Journal
LA English
AB The segment polarity gene cubitus interruptus (ci) encodes a transcriptional effector of **Hedgehog** (Hh) signaling in Drosophila. The Ci gene product is a zinc finger protein belonging to the Gli family of sequence-specific DNA binding proteins. After gastrulation, segmental expression of the segment polarity gene wingless (wg) is maintained by Hh signaling in a **pathway** requiring Ci activity. In the absence of Hh or Ci activity, wg expression is initiated **normally** and then fades in the ectoderm after stage 10. A wingless enhancer region has been previously identified whose Ci binding sites mediate Ci-dependent transcriptional activation in transiently transfected cells. Here it is demonstrated that Hh and **Patched** (Ptc) act through those Ci binding sites to modulate the level of Ci-dependent transcriptional activation in S2 cells. It is also demonstrated that this same wg enhancer region is Hh responsive in vivo and that its Ci binding sites are necessary for its activity. This provides strong evidence that Hh affects wg transcription through post-translational activation of Ci.

L5 ANSWER 35 OF 41 CAPLUS COPYRIGHT 2003 ACS
AN 1997:729385 CAPLUS
DN 128:21263
TI Patched (ptch)-associated preferential expression of smoothened (smoh) in human basal cell carcinoma of the skin
AU Kallassy, Mireille; Toftgard, Rune; Ueda, Masato; Nakazawa, Keiko; Vorechovsky, Igor; Yamasaki, Hiroshi; Nakazawa, Hisayoshi
CS Unit of Multistage Carcinogenesis, IARC, WHO, Lyon, F69372, Fr.
SO Cancer Research (1997), 57(21), 4731-4735
CODEN: CNREA8; ISSN: 0008-5472
PB American Association for Cancer Research
DT Journal
LA English
AB The discovery of specific overexpression of a gatekeeper gene, ptch, in basal cell carcinoma (BCC) led to a hypothesis that the human homolog of **patched** (PTCH) **normally** functions as a neg. regulator of the signaling **pathway** that is initiated by **hedgehogs** (HHs) and activated by the human homolog of smoothened (SMOH); however, no evidence for the involvement of smoh and hhs has been provided. Here, we show novel evidence that smoh is also preferentially overexpressed in BCC, together with ptch, and that Sonic hh was expressed in only some BCCs. Our data, therefore, indicate that such overexpression of smoh may be assocd. with overexpression or mutation of PTCH and that this over-expression subsequently stimulates the PTCH/SMOH signaling **pathway**. In an investigation of a possible regulation of ptch and smoh, we demonstrated that expression of exogenous p21WAF1 in immortalized keratinocytes down-regulates both ptch and smoh and that the down-regulation is accompanied by growth arrest, which suggests the involvement of p21WAF1 in regulation of the PTCH/SMOH signaling **pathway**.

L5 ANSWER 36 OF 41 CAPLUS COPYRIGHT 2003 ACS
AN 1997:690810 CAPLUS
DN 128:2438
TI Activation of the transcription factor Gli1 and the sonic hedgehog signaling pathway in skin tumors
AU Dahmane, N.; Lee, J.; Robins, P.; Heller, P.; Ruiz i Altaba, A.
CS Dev. Genet. Program, Dep. Cell Biol., Skirball Inst., New York Univ. Med. Cent., New York, NY, 10016, USA
SO Nature (London) (1997), 389(6653), 876-881
CODEN: NATUAS; ISSN: 0028-0836
PB Macmillan Magazines
DT Journal
LA English
AB Sporadic basal cell carcinoma (BCC) is the most common type of malignant cancer in fair-skinned adults. Familial BCCS and a fraction of sporadic BCCs have lost the function of **Patched** (Ptc), a Sonic **hedgehog** (Shh) receptor that acts neg. on this signaling **pathway**. Overexpression of Shh can induce BCCs in mice. Here we show that ectopic expression of the zinc-finger transcription factor Gli1 in the embryonic frog epidermis results in the development of tumors that express endogenous Gli1. We also show that Shh and the Gli genes are **normally** expressed in hair follicles, and that human sporadic BCCs consistently express Gli1 but not Shh or Gli3. Because Gli1, but not Gli3, acts as a target and mediator of Shh signaling, our results suggest that expression of Gli1 in basal cells induces BCC formation. Moreover, loss of Ptc or overexpression of Shh cannot be the sole causes of Gli1 induction and sporadic BCC formation, as they do not occur consistently. Thus any mutations leading to the expression of Gli1 in basal cells are predicted to induce BCC formation.

L5 ANSWER 37 OF 41 CAPLUS COPYRIGHT 2003 ACS
AN 1997:593810 CAPLUS
DN 127:275924
TI Evidence for the involvement of the Gli gene family in embryonic mouse lung development
AU Grindley, Justin C.; Bellusci, Saverio; Perkins, Douglas; Hogan, Brigid L. M.
CS Department of Cell Biology, Vanderbilt University Medical Center, Nashville, TN, 37232-2175, USA
SO Developmental Biology (1997), 188(2), 337-348
CODEN: DEBIAO; ISSN: 0012-1606
PB Academic
DT Journal
LA English
AB Murine Gli, Gli2, and Gli3 are zinc finger genes related to Drosophila cubitus interruptus, a component of the **hedgehog** signal transduction **pathway**. In the embryonic lung, all three Gli genes are strongly expressed at the pseudoglandular stage, in distinct but overlapping domains of the mesoderm. Expression of Gli and Gli3, but not of Gli2, is subsequently downregulated at the canalicular stage, coincident with a decline in the expression of sonic **hedgehog** (Shh) and the **hedgehog** receptor gene, **patched** (Ptc). Overexpression of Shh in the lung results in increased levels of Ptc mRNA. Gli, but not Gli2, is also upregulated, suggesting a differential involvement of the Gli genes in the regulation of Ptc by SHH during lung development. Gli3 is not upregulated by Shh overexpression. However, its importance for lung development is shown by the finding that Gli3XtJ embryos, homozygous for a mutation involving a deletion of the Gli3 gene, have a stereotypic pattern of abnormalities in lung morphogenesis. The pulmonary defects in these embryos, consisting of localized shape changes and size redns., correlate with **normal** Gli3 expression. Thus, our data indicate that one of the Gli genes, Gli3, is essential for **normal** lung development, and that another, Gli, can be placed downstream of Shh signaling in the lung.

L5 ANSWER 38 OF 41 CAPLUS COPYRIGHT 2003 ACS
AN 1997:462862 CAPLUS
DN 127:147264
TI A role for ultraspiracle, the Drosophila RXR, in morphogenetic furrow movement and photoreceptor cluster formation
AU Zelhof, Andrew C.; Ghbeish, Nora; Tsai, Chihcheng; Evans, Ronald M.; Mckeown, Michael
CS Molecular Biology and Virology Laboratory, The Salk Institute for Biological Studies, La Jolla, CA, 92037, USA
SO Development (Cambridge, United Kingdom) (1997), 124(13), 2499-2506
CODEN: DEVPED; ISSN: 0950-1991
PB Company of Biologists
DT Journal
LA English
AB Many of the same genes needed for proper eye and limb development in vertebrates, such as hairy, **hedgehog**, **patched** and cAMP-dependent protein kinase A, are responsible for patterning Drosophila imaginal disks, the tissues that will give rise to the adult cuticle structures. This is well demonstrated in the control of morphogenetic furrow movement and differentiation in the eye imaginal disk. The authors report that ultraspiracle, the gene encoding the Drosophila cognate of the Retinoid X Receptor, is required for **normal** morphogenetic furrow movement and ommatidial cluster formation. Examn. of the expression of genes involved in regulating the furrow suggests that ultraspiracle defines a novel regulatory **pathway** in eye differentiation.

L5 ANSWER 39 OF 41 CAPLUS COPYRIGHT 2003 ACS
AN 1997:426937 CAPLUS
DN 127:147718
TI Induction of basal cell carcinoma features in transgenic human skin expressing sonic Hedgehog
AU Fan, Hongran; Oro, Anthony E.; Scott, Matthew P.; Khavari, Paul A.
CS Veterans Affairs Palo Alto Health Care System, Palo Alto, CA, 94304, USA
SO Nature Medicine (New York) (1997), 3(7), 788-792
CODEN: NAMEFI; ISSN: 1078-8956
PB Nature America
DT Journal
LA English
AB **Hedgehog** (HH) signaling proteins mediate inductive events during animal development. Mutation of the only known HH receptor gene, **Patched** (PTC), has recently been implicated in inherited and sporadic forms of the most common human cancer, basal cell carcinoma (BCC). In Drosophila, HH acts by inactivating PTC function, raising the possibility that overexpression of Sonic **Hedgehog** (SHH) in human epidermis might have a tumorigenic effect equiv. to loss of PTC function. The authors used retroviral transduction of **normal** human keratinocytes to constitutively express SHH. SHH-expressing cells demonstrated increased expression of both the known HH target, BMP-2B, as well as bcl-2, a protein prominently expressed by keratinocytes in BCCs. These keratinocytes were then used to regenerate human skin transgenic for long terminal repeat-driven SHH (LTR-SHH) on immune-deficient mice. LTR-SHH human skin consistently displays the abnormal specific histol. features seen in BCCs, including downgrowth of epithelial buds into the dermis, basal cell palisading and sepn. of epidermis from the underlying dermis. In addn., LTR-SHH skin displays the gene expression abnormalities previously described for human BCCs, including decreased BP180/BPAG2 and laminin 5 adhesion proteins and expression of basal epidermal keratins. These data indicate that expression of SHH in human skin recapitulates features of human BCC in vivo, suggest that activation of this conserved signaling **pathway** contributes to the development of epithelial neoplasia and describe a new transgenic human tissue model of neoplasia.

L5 ANSWER 40 OF 41 CAPLUS COPYRIGHT 2003 ACS
AN 1996:561002 CAPLUS
DN 125:218437
TI The role of the human homolog of Drosophila patched in sporadic basal cell carcinomas
AU Gailani, Mae R.; Staahle-Baeckdahl, Mona; Leffell, David J.; Glynn, Michael; Zaphiropoulos, Peter G.; Pressman, Carolyn; Unden, Anne Birgitte; Dean, Michael; Brash, Douglas E.; et al.
CS Dep. Paediatrics, Yale Univ. Sch. Med., New Haven, CT, 06520, USA
SO Nature Genetics (1996), 14(1), 78-81
CODEN: NGENEC; ISSN: 1061-4036
PB Nature Publishing Co.
DT Journal
LA English
AB Basal cell carcinoma (BCC) is the most common cancer in humans. The majority of sporadic BCCs have allelic loss on chromosome 9q22 implying that inactivation of a tumor suppressor in this region is an important step in BCC formation. The gene for nevoid basal cell carcinoma syndrome (NBCCS), an autosomal dominant disorder characterized by multiple BCCs, maps to the same region and is presumed to be the tumor suppressor inactivated at this site. NBCCS has been identified recently and encodes a protein with strong homol. to the Drosophila segment polarity gene, **patched**. Anal. of Drosophila mutants indicates that **patched** interacts with the **hedgehog** signaling **pathway**, repressing the expression of various **hedgehog** target genes including wingless, decapentaplegic and **patched** itself. Using single strand conformational polymorphism (SSCP) to screen human **patched** in 37 sporadic BCCs, the authors detected mutations in one-third of the tumors. Direct sequencing of two BCCs without SSCP variants revealed mutations in those tumors as well suggesting that inactivation of **patched** is probably a necessary step in BCC development. Northern blots and RNA in situ hybridization showed that **patched** is expressed at high levels in tumor cells but not **normal** skin suggesting that mutational inactivation of the gene leads to overexpression of mutant transcript owing to failure of a neg. feedback mechanism.

L5 ANSWER 41 OF 41 CAPLUS COPYRIGHT 2003 ACS
AN 1996:19089 CAPLUS
DN 124:51157
TI Patched overexpression alters wing disk size and pattern: transcriptional and post-transcriptional effects on hedgehog targets
AU Johnson, Ronald L.; Grenier, Jennifer K.; Scott, Matthew P.
CS Howard Hughes Med. Inst., Stanford Univ. Sch. Med., Stanford, CA, 94305-5427, USA
SO Development (Cambridge, United Kingdom) (1995), 121(12), 4161-70
CODEN: DEVPED; ISSN: 0950-1991
PB Company of Biologists
DT Journal
LA English
AB The membrane protein, **Patched**, plays a crit. role in patterning embryonic and imaginal tissues in Drosophila. **Patched** constitutively inactivates the transcription of target genes such as wingless, decapentaplegic, and **patched** itself. The secreted protein, **Hedgehog**, induces transcription of target genes by opposing the **Patched** signaling **pathway**. Using the Gal4 UAS system we have overexpressed gene **patched** in wing imaginal disks and found that high **Patched** levels, expressed in either **normal** or ectopic patterns, result in loss of wing vein patterning in both compartments centering at the anterior/posterior border. In addn., **patched** inhibits the formation of the mechanosensory neurons, the campaniform sensilla, in the wing blade. The **patched** wing vein phenotype is modulated by mutations in **hedgehog** and cubitus interruptus (ci). **Patched** overexpression inhibits transcription of **patched** and decapentaplegic and post-transcriptionally decreases the amt. of Ci protein at the anterior/posterior boundary. In **hedgehogMrt** wing disks, which express ectopic **hedgehog**, Ci levels are correspondingly elevated, suggesting that **hedgehog** relieves **patched** repression of Ci accumulation. Protein kinase A also regulates Ci; protein kinase A mutant clones in the anterior compartment have increased levels of Ci protein. Thus **patched** influences wing disk patterning by decreasing Ci protein levels and inactivating **hedgehog** target genes in the anterior compartment.

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=> s inhibit?
L6     1572014 INHIBIT?

=> s l1(l)l6
L7         121 L1(L)L6

=> s cell?
L8     2664295 CELL?

=> s l7(l)l8
L9          81 L7(L)L8

=> s l2(l)l9
L10         21 L2(L)L9

=> s l10 not l5
L11         11 L10 NOT L5

=> d l11 1-11 bib,ab
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L11 ANSWER 1 OF 11 CAPLUS COPYRIGHT 2003 ACS
AN 2003:291279 CAPLUS
TI GSK-3: Tricks of the trade for a multi-tasking kinase
AU Doble, Bradley W.; Woodgett, James R.
CS Ontario Cancer Institute, Toronto, ON, M5G 2M9, Can.
SO Journal of Cell Science (2003), 116(7), 1175-1186
CODEN: JNCSAI; ISSN: 0021-9533
PB Company of Biologists Ltd.
DT Journal
LA English
AB Glycogen synthase kinase 3 (GSK-3) is a multifunctional serine/threonine kinase found in all eukaryotes. The enzyme is a key regulator of numerous signalling **pathways**, including **cellular** responses to Wnt, receptor tyrosine kinases and G-protein-coupled receptors and is involved in a wide range of **cellular** processes, ranging from glycogen metab. to **cell** cycle regulation and proliferation. GSK-3 is unusual in that it is **normally** active in **cells** and is primarily regulated through **inhibition** of its activity. Another peculiarity compared with other protein kinases is its preference for primed substrates, i.e., substrates previously phosphorylated by another kinase. Several recent advances have improved our understanding of GSK-3 regulation in multiple **pathways**. These include the soln. of the crystal structure of GSK-3, which has provided insight into GSK-3's penchant for primed substrates and the regulation of GSK-3 by serine phosphorylation, and findings related to the involvement of GSK-3 in the Wnt/.beta.-catenin and **Hedgehog pathways**. Finally, since increased GSK-3 activity may be linked to pathol. in diseases such as Alzheimer's disease and non-insulin-dependent diabetes mellitus, several new GSK-3 **inhibitors**, such as the aloisines, the paullones and the maleimides, have been developed. Although they are just starting to be characterized in **cell** culture expts., these new **inhibitors** hold promise as therapeutic agents.
RE.CNT 160 THERE ARE 160 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 2 OF 11 CAPLUS COPYRIGHT 2003 ACS
AN 2003:117561 CAPLUS
DN 138:163512
TI Mediators of hedgehog signaling pathways, compositions, and uses related thereto
IN Rubin, Lee; Guicherit, Oivin M.; Price, Stephen; Boyd, Edward A.
PA Curis, Inc., USA
SO PCT Int. Appl., 168 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2003011219	A2	20030213	WO 2002-US24073	20020729

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRAI US 2001-308449P P 20010727
US 2001-338031P P 20011113
OS MARPAT 138:163512
AB The invention provides methods and reagents for **inhibiting** aberrant growth states resulting from **hedgehog** gain-of-function, ptc loss-of-function or smoothened gain-of-function, comprising contacting the **cell** with a **hedgehog** antagonist, such as a small mol., in a sufficient amt. to aberrant growth state, e.g.,to agonize a **normal** ptc **pathway** or antagonize smoothened or **hedgehog** activity. Prepn. and testing of a variety of heterocyclic compds. is included. The effect of benzimidazole deriv. I on a variety of tumor **cells** (e.g. basal **cell** carcinoma) was detd.

L11 ANSWER 3 OF 11 CAPLUS COPYRIGHT 2003 ACS
AN 2002:978471 CAPLUS
DN 138:39182
TI Preparation of substituted benzothiophene derivatives as hedgehog agonists and regulators of cell proliferation and differentiation
IN Baxter, Anthony David; Boyd, Edward Andrew; Guicherit, Oivin M.; Porter, Jeffery; Price, Stephen; Rubin, Lee; Stibbard, John Harry Alexander
PA UK
SO U.S. Pat. Appl. Publ., 130 pp., Cont.-in-part of U.S. Ser. No. 724,492.
CODEN: USXXCO
DT Patent
LA English
FAN.CNT 2

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI US 2002198236	A1	20021226	US 2001-964276	20010926
WO 2003027234	A2	20030403	WO 2002-US29522	20020918

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRAI	US 2000-193279P	P	20000330
	US 2000-724492	A2	20001128
	US 2001-964276	A	20010926

OS MARPAT 138:39182
AB Title compds. I [Ar = (hetero)aryl; X = CO, CS, SO2, SO, CH2; Y = absent; Z = absent, aryl, carbocyclyl, heterocyclyl, etc.; M = (un)substituted methylene, etc.; Cy = aryl, heterocyclyl, heteroaryl, cycloalkyl; Cy' = 3-chlorobenzo[b]thiophen-2-yl, 3-fluorobenzo[b]thiophen-2-yl, etc.] are prepd. For instance, N-(4-aminocyclohexyl)-N-methylcarbamic acid tert-Bu ester (prepn. given) was alkylated with 5'-formyl-2'-methoxy-[1,1'-Biphenyl]-4-carbonitrile (MeO3CH, NaBH(OAc)3) and the resulting adduct acylated with 3-chlorobenzo[b]thiophene-2-carbonyl chloride and finally deprotected to give II, which was isolated as the hydrochloride. Methods and reagents are provided for modulating proliferation or differentiation in a **cell** or tissue, comprising contacting the **cell** with a **hedgehog** agonist. I are used to correct or **inhibit** an aberrant or unwanted growth state, e.g., by antagonizing a **normal** ptc **pathway** or agonizing smoothened or **hedgehog** activity.

L11 ANSWER 4 OF 11 CAPLUS COPYRIGHT 2003 ACS
AN 2002:293442 CAPLUS
DN 136:325823
TI Preparation and formulation of proline derivatives as mediators of hedgehog signaling pathways for pharmaceutical and cosmetic uses
IN Baxter, Anthony D.; Boyd, Edward A.; Guicherit, Oivin M.; Price, Stephen; Rubin, Lee D.
PA Curis, Inc., USA
SO PCT Int. Appl., 230 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 4

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002030421	A2	20020418	WO 2001-US32054	20011012
	WO 2002030421	A3	20020926		
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	US 6552016	B1	20030422	US 2000-688018	20001013
	AU 2002011713	A5	20020422	AU 2002-11713	20011012
	US 2002165221	A1	20021107	US 2001-977096	20011012
PRAI	US 2000-240536P	P	20001013		
	US 1999-159417P	P	19991014		
	US 2000-196543P	P	20000411		
	US 2000-211919P	P	20000616		
	US 2000-240564P	P	20001013		
	WO 2001-US32054	W	20011012		

OS MARPAT 136:325823
AB Proline-based compds. such as I [R1, R4 = H, alkyl, (CH2)n-(hetero)aryl (n = 0-5); L = null, -(CH2)n-, -alkenyl-, -alkynyl-, -(CH2)n-alkenyl-, -(CH2)n-alkynyl-, -(CH2)nO(CH2)p-, -(CH2)nNR8(CH2)p-, -(CH2)nS(CH2)p-, -(CH2)nalkenyl(CH2)p-, -(CH2)nalkynyl(CH2)p-, -O(CH2)n-,-NR8(CH2)n-, or -S(CH2)n- (R8 is any group given for R1 or two R8 together may form a 4- to 8-membered ring; p = 0-3); X, D = NR8, O, S, NR8NR8, ONR8, or a direct bond; Y, Z = O or S; E represents NR5, where R5 represents LR8 or an ammonium salt; X1, X2 = null, CH2 or CH2CH2] were prepd. for pharmaceutical and cosmetic use. Thus, proline deriv. II was prepd. via a multistep synthetic sequence which started with trans-4-hydroxy-L-proline, 3-methoxybenzaldehyde, piperonal, tert-butylacetyl chloride, and N-(tert-butoxycarbonyl)piperazine. The prepd. proline derivs. were tested for agonist activity for **inhibiting** aberrant growth states resulting from **hedgehog** gain-of-function, ptc loss-of-function or smoothened gain-of-function comprising contacting the **cell** with a **hedgehog** antagonist, such as a small mol., in a sufficient amt. to aberrant growth state, e.g., to agonize a **normal** ptc **pathway** or antagonize smoothened or **hedgehog** activity.

L11 ANSWER 5 OF 11 CAPLUS COPYRIGHT 2003 ACS
AN 2001:905689 CAPLUS
DN 136:99869
TI BMP and Ihh/PTHrP signaling interact to coordinate chondrocyte proliferation and differentiation
AU Minina, Eleonora; Wenzel, Hans Markus; Kreschel, Conny; Karp, Seth; Gaffield, William; McMahon, Andrew P.; Vortkamp, Andrea
CS Otto Warburg-Laboratory, Max-Planck-Institute for Molecular Genetics, Berlin, 14195, Germany
SO Development (Cambridge, United Kingdom) (2001), 128(22), 4523-4534
CODEN: DEVPED; ISSN: 0950-1991
PB Company of Biologists Ltd.
DT Journal
LA English
AB During endochondral ossification, two secreted signals, Indian **hedgehog** (Ihh) and parathyroid hormone-related protein (PTHrP), have been shown to form a neg. feedback loop regulating the onset of hypertrophic differentiation of chondrocytes. Bone morphogenetic proteins (BMPs), another family of secreted factors regulating bone formation, have been implicated as potential interactors of the Ihh/PTHrP feedback loop. To analyze the relationship between the two signaling **pathways**, we used an organ culture system for limb explants of mouse and chick embryos. We manipulated chondrocyte differentiation by supplementing these cultures either with BMP2, PTHrP and Sonic **hedgehog** as activators or with Noggin and cyclopamine as **inhibitors** of the BMP and Ihh/PTHrP signaling systems. Overexpression of Ihh in the cartilage elements of transgenic mice results in an upregulation of PTHrP expression and a delayed onset of hypertrophic differentiation. Noggin treatment of limbs from these mice did not antagonize the effects of Ihh overexpression. Conversely, the promotion of chondrocyte maturation induced by cyclopamine, which blocks Ihh signaling, could not be rescued with BMP2. Thus BMP signaling does not act as a secondary signal of Ihh to induce PTHrP expression or to delay the onset of hypertrophic differentiation. Similar results were obtained using cultures of chick limbs. We further investigated the role of BMP signaling in regulating proliferation and hypertrophic differentiation of chondrocytes and identified three functions of BMP signaling in this process. First we found that maintaining a **normal** proliferation rate requires BMP and Ihh signaling acting in parallel. We further identified a role for BMP signaling in modulating the expression of Ihh. Finally, the application of Noggin to mouse limb explants resulted in advanced differentiation of terminally hypertrophic **cells**, implicating BMP signaling in delaying the process of hypertrophic differentiation itself. This role of BMP signaling is independent of the Ihh/PTHrP **pathway**.
RE.CNT 59 THERE ARE 59 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 6 OF 11 CAPLUS COPYRIGHT 2003 ACS
AN 2001:815731 CAPLUS
DN 136:67162
TI Notch signalling and the initiation of neural development in the Drosophila eye
AU Baonza, Antonio; Freeman, Matthew
CS MRC Laboratory of Molecular Biology, Cambridge, CB2 2QH, UK
SO Development (Cambridge, United Kingdom) (2001), 128(20), 3889-3898
CODEN: DEVPED; ISSN: 0950-1991
PB Company of Biologists Ltd.
DT Journal
LA English
AB Neural detn. in the Drosophila eye occurs progressively. A diffusible signal, Dpp, causes undetd. **cells** first to adopt a "pre-proneural" state in which they are primed to start differentiating. A second signal is required to trigger the activation of the transcription factor Atonal, which causes the **cells** to initiate overt photoreceptor neuron differentiation. Both Dpp and the second signal are dependent on **Hedgehog** (Hh) signaling. Previous work has shown that the Notch signaling **pathway** also has a proneural role in the eye (as well as a later, opposite function when it restricts the no. of **cells** becoming photoreceptors - a process of lateral **inhibition**). It is not clear how the early proneural role of Notch integrates with the other signaling **pathways** involved. The authors provide evidence that Notch activation by its ligand Delta is the second Hh-dependent signal required for neural detn. Notch activity **normally** only triggers Atonal expression in **cells** that have adopted the pre-proneural state induced by Dpp. The authors also report that Notch drives the transition from pre-proneural to proneural by downregulating two repressors of Atonal: Hairy and Extramacrochaetae.
RE.CNT 60 THERE ARE 60 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 7 OF 11 CAPLUS COPYRIGHT 2003 ACS
AN 2001:747593 CAPLUS
DN 135:283224
TI Small organic molecule hedgehog agonists as regulators of cell proliferation and differentiation
IN Baxter, Anthony David; Boyd, Edward Andrew; Guicherit, Oivin M.; Porter, Jeffrey; Price, Stephen; Rubin, Lee E.
PA Curis, Inc., USA
SO PCT Int. Appl., 246 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 2

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2001074344	A2	20011011	WO 2001-US10296	20010330
WO 2001074344	A3	20020523		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1272168	A2	20030108	EP 2001-922914	20010330
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				

PRAI US 2000-193279P P 20000330
US 2000-724492 A 20001128
US 2000-724955 A 20001128
WO 2001-US10296 W 20010330
OS MARPAT 135:283224
AB Methods and reagents are provided for modulating proliferation or differentiation in a **cell** or tissue, comprising contacting the **cell** with a **hedgehog** agonist. In certain embodiments, the methods and reagents may be employed to correct or **inhibit** an aberrant or unwanted growth state, e.g., by antagonizing a **normal** ptc **pathway** or agonizing smoothened or **hedgehog** activity. Prepn. of compds. (e.g. I) is described.

L11 ANSWER 8 OF 11 CAPLUS COPYRIGHT 2003 ACS
AN 2001:283777 CAPLUS
DN 134:311102
TI Preparation and formulation of heterocycles as mediators of hedgehog signaling pathways for pharmaceutical and cosmetic uses
IN Baxter, Anthony David; Boyd, Edward Andrew; Guicherit, Oivin M.; Price, Stephen; Rubin, Lee
PA Curis, Inc., USA
SO PCT Int. Appl., 219 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 4

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001026644	A2	20010419	WO 2000-US28579	20001013
	WO 2001026644	A3	20020418		
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	EP 1227805	A2	20020807	EP 2000-978225	20001013
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				
	JP 2003511411	T2	20030325	JP 2001-529434	20001013
	US 6552016	B1	20030422	US 2000-688018	20001013
PRAI	US 1999-159417P	P	19991014		
	US 2000-196543P	P	20000411		
	US 2000-211919P	P	20000616		
	US 2000-240536P	P	20001013		
	WO 2000-US28579	W	20001013		

OS MARPAT 134:311102
AB Heterocycles, such as I [E = O, S, NR; D, X = NR2, O, S, bond, etc.; L = linking group, such as alkylene, alkenylene, alkynylene; XL = piperazin-1,4-diyl, etc.; R, R1, R2 = H, alkyl, acyl, arylalkyl, heteroarylalkyl, etc.], were prepd. for pharmaceutical and cosmetic use. Thus, pyrrolidine II was prepd. via a multistep synthetic sequence which started with trans-4-hydroxy-L-proline, 3-methoxybenzaldehyde, piperonal, tert-butylacetyl chloride, and N-(tert-butoxycarbonyl)piperazine. The prepd. pyrrolidines were tested for agonist activity for **inhibiting** aberrant growth states resulting from **hedgehog** gain-of-function, ptc loss-of-function or smoothened gain-of-function comprising contacting the **cell** with a **hedgehog** antagonist, such as a small mol., in a sufficient amt. to aberrant growth state, e.g., to agonize a **normal** ptc **pathway** or antagonize smoothened or **hedgehog** activity.

L11 ANSWER 9 OF 11 CAPLUS COPYRIGHT 2003 ACS
AN 1998:336818 CAPLUS
DN 129:91227
TI Noggin-mediated antagonism of BMP signaling is required for growth and patterning of the neural tube and somite
AU Mcmahon, Jill A.; Takada, Shinji; Zimmerman, Lyle B.; Fan, Chen-Ming; Harland, Richard M.; Mcmahon, Andrew P.
CS Department of Molecular and Cellular Biology, Harvard University, Cambridge, MA, 02138, USA
SO Genes & Development (1998), 12(10), 1438-1452
CODEN: GEDEEP; ISSN: 0890-9369
PB Cold Spring Harbor Laboratory Press
DT Journal
LA English
AB Embryonic patterning in vertebrates is dependent upon the balance of inductive signals and their specific antagonists. We show that Noggin, which encodes a bone morphogenetic protein (BMP) antagonist expressed in the node, notochord, and dorsal somite, is required for **normal** mouse development. Although Noggin has been implicated in neural induction, examn. of null mutants in the mouse indicates that Noggin is not essential for this process. However, Noggin is required for subsequent growth and patterning of the neural tube. Early BMP-dependent dorsal **cell** fates, the roof plate and neural crest, form in the absence of Noggin. However, there is a progressive loss of early, Sonic **hedgehog** (Shh)-dependent ventral **cell** fates despite the **normal** expression of Shh in the notochord. Further, somite differentiation is deficient in both muscle and sclerotomal precursors. Addn. of BMP2 or BMP4 to paraxial mesoderm explants blocks Shh-mediated induction of Pax-1, a sclerotomal marker, whereas addn. of Noggin is sufficient to induce Pax-1. Noggin and Shh induce Pax-1 synergistically. Use of protein kinase A stimulators blocks Shh-mediated induction of Pax-1, but not induction by Noggin, suggesting that induction is mediated by different **pathways**. Together these data demonstrate that **inhibition** of BMP signaling by axially secreted Noggin is an important requirement for **normal** patterning of the vertebrate neural tube and somite.
RE.CNT 77 THERE ARE 77 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 10 OF 11 CAPLUS COPYRIGHT 2003 ACS
AN 1997:594414 CAPLUS
TI Left/right patterning signals and the independent regulation of different aspects of situs in the chick embryo
AU Levin, Michael; Pagan, Sylvia; Roberts, Drucilla J.; Cooke, Jonathan; Kuehn, Michael R.; Tabin, Clifford J.
CS Department of Genetics, Harvard Medical School, Boston, MA, 02115, USA
SO Developmental Biology (1997), 189(1), 57-67
CODEN: DEBIAO; ISSN: 0012-1606
PB Academic
DT Journal
LA English
AB Recently, a **pathway** of genes which are part of a cascade regulating the side on which the heart forms during chick development was characterized (M. Levin et al., 1995, **Cell** 82, 1-20). Here we extend these previous studies, showing that manipulation of at least one member of the cascade, Sonic **hedgehog** (Shh), can affect the situs of embryonic rotation and of the gut, in addn. to the heart. Bilateral expression of Shh, which is **normally** found exclusively on the left, does not result in left isomerism (a bilaterally sym. embryo having two left sides) nor in a complete situs inversus phenotype. Instead, misexpression of Shh on the right side of the node, which in turn leads to bilateral nodal expression, produces a heterotaxia-like condition, where different aspects of laterality are detd. independently. Heart situs has previously been shown to be altered by ectopic Shh and activin. However, the most downstream gene identified in the LR **pathway**, nodal, had not been functionally linked to heart laterality. We show that ectopic (right-sided) nodal expression is able to affect heart situs, suggesting that the randomization of heart laterality obsd. in Shh and activin misexpression expts. is a result of changes in nodal expression and that nodal is likely to regulate heart situs endogenously. The first defined asym. signal in the left-right patterning **pathway** is Shh, which is initially expressed throughout Hensen's node but becomes restricted to the left side at stage 4+. It has been hypothesized that the restriction of Shh expression may be due to repression by an upstream activin-like factor. The involvement of such an activin-like factor on the right side of Hensen's node was suggested because ectopic activin protein is able to repress Shh on the left side of the node, as well as to induce ectopic expression of a **normally** right-sided marker, the activin receptor cAct-RIIa. Here we provide further evidence in favor of this model. We find that a member of this family, Activin .beta.B, is indeed expressed asym., only on the right side of Hensen's node, at the correct time for it to be the endogenous asym. activin signal. Furthermore, we show that application of follistatin-loaded beads eliminates the asymmetry in Shh expression, consistent with an **inhibition** of an endogenous member of the activin-BMP superfamily. This combined with the previous data on exogenous activin supports the model that Activin .beta.B functions in the chick embryo to initiate Shh asymmetry. While these data extend our understanding of the early signals which establish left-right asymmetry, they leave unanswered the interesting question of how the bilateral symmetry of the embryo is initially broken to define a consistent left-right axis. Anal. of spontaneous chick twins suggests that, whatever the mol. mechanism, left-right patterning is unlikely to be due to a blastodermal prepattern but rather is initiated in a streak-autonomous manner.

L11 ANSWER 11 OF 11 CAPLUS COPYRIGHT 2003 ACS
AN 1996:668482 CAPLUS
TI Restoration of the organizer after radical ablation of Hensen's node and the anterior primitive streak in the chick embryo
AU Psychoyos, Delphine; Stern, Claudio D.
CS Dep. Genetics and Dev., Columbia Univ., New York, NY, 10032, USA
SO Development (Cambridge, United Kingdom) (1996), 122(10), 3263-3273
CODEN: DEVPED; ISSN: 0950-1991
PB Company of Biologists
DT Journal
LA English
AB The region of the amniote embryo corresponding to Spemann's organizer in amphibians is Hensen's node, which lies at the tip of the primitive streak during gastrulation. It is a special site in the embryo that can be defined by the presence of progenitors of several axial tissues (notochord, prechordal mesoderm, somites, gut endoderm), by characteristic **cell** movements, by specific patterns of gene expression (e.g. goosecoid, HNF-3.beta., Sonic **hedgehog**) and, most importantly, by its ability to induce a complete axis, including host-derived neural tissue, when transplanted to an ectopic site. Here, we show that complete removal not only of the node but also of the anterior 40% of the primitive streak leads to the development of **normal** embryos contg. **cells** with all the fates **normally** produced by the node. **Cell** movement **pathways** through the regenerated node are identical to those seen in the **normal** embryo. The patterns of expression of HNF-3.beta. and Sonic **hedgehog** are also restored, as is their left/right asymmetry, but goosecoid expression is not. When the regenerated node is transplanted to an ectopic site, it induces a complete embryonic axis that includes a fully patterned, host-derived central nervous system. Anal. of the properties of **cell** surrounding the site of ablation shows that they acquire these properties gradually. We suggest that the organizer is a region of the embryo that is defined by **cell** interactions and that the node **normally inhibits** the organize state in neighboring **cells**.

```
=> s amu
L12        3925 AMU

=> d his

     (FILE 'HOME' ENTERED AT 10:44:31 ON 19 MAY 2003)

     FILE 'CAPLUS' ENTERED AT 10:44:36 ON 19 MAY 2003
L1           550 S HEDGEHOG? (L) PATHWAY?
L2        941844 S NORMAL?
L3           110 S L1(L)L2
L4           865 S PATCHED?
L5            41 S L3(L)L4

     FILE 'STNGUIDE' ENTERED AT 10:46:30 ON 19 MAY 2003

     FILE 'CAPLUS' ENTERED AT 10:50:21 ON 19 MAY 2003
L6       1572014 S INHIBIT?
L7           121 S L1(L)L6
L8       2664295 S CELL?
L9            81 S L7(L)L8
L10           21 S L2(L)L9
L11           11 S L10 NOT L5
L12         3925 S AMU

=> s l7(l)l12
L13           0 L7(L)L12

=> s l7 (p) l12
PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH
FIELD CODE - 'AND' OPERATOR ASSUMED 'L7 (P) L12'
L14           0 L7 (P) L12

=> s l7 and l12
L15           0 L7 AND L12

=> s molecular weight
         935863 MOLECULAR
          93088 WEIGHT
L16       52160 MOLECULAR WEIGHT
                (MOLECULAR(W)WEIGHT)

=> s l7(l)l16
L17           0 L7(L)L16

=> s l7(l)l4
L18          43 L7(L)L4

=> s l18 not l5
L19          30 L18 NOT L5

=> s l19 not l11
L20          30 L19 NOT L11

=> d l20 1-30 bib,ab
```

L20 ANSWER 1 OF 30 CAPLUS COPYRIGHT 2003 ACS
AN 2003:252192 CAPLUS
TI Several Human PATCHED1 Mutations Block Protein Maturation
AU Bailey, Evans C.; Zhou, Lei; Johnson, Ronald L.
CS Departments of Cell Biology and Neurobiology, University of Alabama at Birmingham, Birmingham, AL, 35294-0005, USA
SO Cancer Research (2003), 63(7), 1636-1638
CODEN: CNREA8; ISSN: 0008-5472
PB American Association for Cancer Research
DT Journal
LA English
AB The tumor suppressor gene **PATCHED1** (PTCH1) is mutated in sporadic and inherited forms of basal cell carcinoma. PTCH1 binds **Hedgehog** proteins and **inhibits** signaling in the absence of ligand. Although PTCH1 mutations are proposed to reduce or abolish protein function, few mutations have been tested for activity. We introduced six PTCH1 missense mutations into mouse **patched1** and tested them in murine cells deficient for **patched1** function. Three mutants retained significant activity. Three other mutants had little or no function, and of these, two were retained in the secretory **pathway**. These studies indicate that missense mutations can abolish PTCH1 function by blocking protein maturation.

L20 ANSWER 2 OF 30 CAPLUS COPYRIGHT 2003 ACS
AN 2003:235203 CAPLUS
TI A retinoic acid receptor-selective agonist causes jaw deformity in the Japanese flounder, Paralichthys olivaceus
AU Haga, Y.; Suzuki, T.; Kagechika, H.; Takeuchi, T.
CS Department of Aquatic Biosciences, Tokyo University of Fisheries, 4-5-7 Konan, Minato-ku, Tokyo, 108-8477, Japan
SO Aquaculture (2003), 221(1-4), 381-392
CODEN: AQCLAL; ISSN: 0044-8486
PB Elsevier Science B.V.
DT Journal
LA English
AB We examd. the effects of synthetic retinoids on the jaw development of Japanese flounder during postembryonic development. Flounder larvae were exposed to Am80 [a retinoic acid receptor (RAR).alpha./.beta.-selective retinoid] and methoprene acid [MA, a retinoid X receptor (RXR)-selective retinoid]. Am80 induced lower jaw deformities in all fish, whereas MA induced lower jaw deformities in less than 20% of the fish. Am80 caused drastic deformities in the upper jaw as well as the lower jaw, while MA did not affect the upper jaw. RT-PCR anal. of the lower jaw revealed that RAR expression was greatly increased by Am80 treatment. Expression of **patched** (ptc) which is a receptor of the **hedgehog** family, was **inhibited** by both Am80 and MA treatments. Immunohistochem. using anti-RAR.alpha.-antibody revealed that RAR.alpha.-pos. osteoblasts exist around the jaw bones. We propose that disturbance of the RAR signaling **pathway** regulating osteoblast activity is mainly responsible for the jaw deformities.

L20 ANSWER 3 OF 30 CAPLUS COPYRIGHT 2003 ACS
AN 2003:93513 CAPLUS
TI Small-molecule modulators of Hedgehog signaling: identification and characterization of Smoothened agonists and antagonists
AU Frank-Kamenetsky, Maria; Zhang, Xiaoyan M.; Bottega, Steve; Guicherit, Oivin; Wichterle, Hynek; Dudek, Henryk; Bumcrot, David; Wang, Frank Y.; Jones, Simon; Shulok, Janine; Rubin, Lee L.; Porter, Jeffery A.
CS Curtis, Inc., Cambridge, MA, 02138, USA
SO Journal of Biology (London, United Kingdom) (2002), 1(2), No pp. given
CODEN: JBOIAW; ISSN: 1475-4924
URL: http://jbiol.com/content/1/2/10
PB BioMed Central Ltd.
DT Journal; (online computer file)
LA English
AB Background: The **Hedgehog** (Hh) signaling **pathway** is vital to animal development as it mediates the differentiation of multiple cell types during embryogenesis. In adults, Hh signaling can be activated to facilitate tissue maintenance and repair. Moreover, stimulation of the Hh **pathway** has shown therapeutic efficacy in models of neuropathy. The underlying mechanisms of Hh signal transduction remain obscure, however: little is known about the communication between the **pathway** suppressor **Patched** (Ptc), a multipass transmembrane protein that directly binds Hh, and the **pathway** activator Smoothened (Smo), a protein that is related to G-protein-coupled receptors and is capable of constitutive activation in the absence of Ptc. Results: We have identified and characterized a synthetic non-peptidyl small mol., Hh-Ag, that acts as an agonist of the Hh **pathway**. This Hh agonist promotes cell-type-specific proliferation and concn.-dependent differentiation in vitro, while in utero it rescues aspects of the Hh-signaling defect in Sonic **hedgehog**-null, but not Smo-null, mouse embryos. Biochem. studies with Hh-Ag, the Hh-signaling antagonist cyclopamine, and a novel Hh-signaling **inhibitor** Cur61414, reveal that the action of all these compds. is independent of Hh-protein ligand and of the Hh receptor Ptc, as each binds directly to Smo. Conclusions: Smo can have its activity modulated directly by synthetic small mols. These studies raise the possibility that Hh signaling may be regulated by endogenous small mols. in vivo and provide potent compds. with which to test the therapeutic value of activating the Hh-signaling **pathway** in the treatment of traumatic and chronic degenerative conditions.
RE.CNT 52 THERE ARE 52 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 4 OF 30 CAPLUS COPYRIGHT 2003 ACS
AN 2002:955088 CAPLUS
TI Sonic hedgehog regulates proliferation and differentiation of mesenchymal cells in the mouse metanephric kidney
AU Yu, Jing; Carroll, Thomas J.; McMahon, Andrew P.
CS Department of Molecular and Cellular Biology, Harvard University, Cambridge, MA, 02138, USA
SO Development (Cambridge, United Kingdom) (2002), 129(22), 5301-5312
CODEN: DEVPED; ISSN: 0950-1991
PB Company of Biologists Ltd.
DT Journal
LA English
AB Signaling by the ureteric bud epithelium is essential for survival, proliferation and differentiation of the metanephric mesenchyme during kidney development. Most studies that have addressed ureteric signaling have focused on the proximal, branching, ureteric epithelium. We demonstrate that sonic **hedgehog** is expressed in the ureteric epithelium of the distal, non-branching medullary collecting ducts and continues into the epithelium of the ureter - the urinary outflow tract that connects the kidney with the bladder. Upregulation of **patched** 1, the sonic **hedgehog** receptor and a downstream target gene of the signaling **pathway** in the mesenchyme surrounding the distal collecting ducts and the ureter suggests that sonic **hedgehog** acts as a paracrine signal. In vivo and in vitro analyses demonstrate that sonic **hedgehog** promotes mesenchymal cell proliferation, regulates the timing of differentiation of smooth muscle progenitor cells, and sets the pattern of mesenchymal differentiation through its dose-dependent **inhibition** of smooth muscle formation. In addn., we also show that bone morphogenetic protein 4 is a downstream target gene of sonic **hedgehog** signaling in kidney stroma and ureteral mesenchyme, but does not mediate the effects of sonic **hedgehog** in the control of mesenchymal proliferation.
RE.CNT 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 5 OF 30 CAPLUS COPYRIGHT 2003 ACS
AN 2002:548057 CAPLUS
DN 137:260411
TI Sonic Hedgehog Induces the Segregation of Patched and Smoothened in Endosomes
AU Incardona, John P.; Gruenberg, Jean; Roelink, Henk
CS Department of Biological Structure and Center for Developmental Biology, University of Washington, Seattle, WA, 98195, USA
SO Current Biology (2002), 12(12), 983-995
CODEN: CUBLE2; ISSN: 0960-9822
PB Cell Press
DT Journal
LA English
AB Background: Sonic **hedgehog** (Shh) signal transduction involves the ligand binding **Patched1** (Ptc1) protein and a signaling component, Smoothened (Smo). A select group of compds. **inhibits** both Shh signaling, regulated by Ptc1, and late endosomal lipid sorting, regulated by the Ptc-related Niemann-Pick C1 (NPC1) protein. This suggests that Ptc1 regulates Smo activity through a common late endosomal sorting **pathway** also utilized by NPC1. During signaling, Ptc accumulates in endosomal compartments, but it is unclear if Smo follows Ptc into the endocytic **pathway**. Results: We characterized the dynamic subcellular distributions of Ptc1, Smo, and activated Smo mutants individually and in combination. Ptc1 and Smo colocalize extensively in the absence of ligand and are internalized together after ligand binding, but Smo becomes segregated from Ptc1/Shh complexes destined for lysosomal degrdn. In contrast, activated Smo mutants do not colocalize with nor are cotransported with Ptc1. Agents that block late endosomal transport and protein sorting **inhibit** the ligand-induced segregation of Ptc1 and Smo. We show that, like NPC1-regulated lipid sorting, Shh signal transduction is blocked by antibodies that specifically disrupt the internal membranes of late endosomes, which provide a platform for protein and lipid sorting. Conclusions: These data support a model in which Ptc1 **inhibits** Smo only when in the same compartment. Ligand-induced segregation allows Smo to signal independently of Ptc1 after becoming sorted from Ptc1/Shh complexes in the late endocytic **pathway**.
RE.CNT 51 THERE ARE 51 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 6 OF 30 CAPLUS COPYRIGHT 2003 ACS
AN 2002:362359 CAPLUS
DN 137:122426
TI Hedgehog regulates cell growth and proliferation by inducing Cyclin D and Cyclin E
AU Duman-Scheel, Molly; Weng, Li; Xin, Shijie; Du, Wei
CS Ben May Institute for Cancer Research and Center for Molecular Oncology, The University of Chicago, Chicago, IL, 60637, USA
SO Nature (London, United Kingdom) (2002), 417(6886), 299-304
CODEN: NATUAS; ISSN: 0028-0836
PB Nature Publishing Group
DT Journal
LA English
AB Although mutations that activate the **Hedgehog** (Hh) signaling **pathway** have been linked to several types of cancer, the mol. and cellular basis of Hh's ability to induce tumor formation is not well understood. The authors identified a mutation in **patched** (ptc), an **inhibitor** of Hh signaling, in a genetic screen for regulators of the Retinoblastoma (Rb) **pathway** in Drosophila. Here Hh signaling promotes transcription of Cyclin E and Cyclin D, two **inhibitors** of Rb, and principal regulators of the cell cycle during development in Drosophila. Upregulation of Cyclin E expression, accomplished through binding of Cubitus interruptus (Ci) to the Cyclin E promoter, mediates the ability of Hh to induce DNA replication. Upregulation of Cyclin D expression by Hh mediates the distinct ability of Hh to promote cellular growth. The discovery of a direct connection between Hh signaling and principal cell-cycle regulators provides insight into the mechanism by which deregulated Hh signaling promotes tumor formation.
RE.CNT 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 7 OF 30 CAPLUS COPYRIGHT 2003 ACS
AN 2002:340500 CAPLUS
DN 137:288620
TI Introduction of wild-type patched gene suppresses the oncogenic potential of human squamous cell carcinoma cell lines including A431
AU Koike, Chika; Mizutani, Taketoshi; Ito, Taiji; Shimizu, Yasuhito; Yamamichi, Nobutake; Kameda, Takashi; Michimukai, Eiji; Kitamura, Naoya; Okamoto, Tetsuji; Iba, Hideo
CS Department of Microbiology and Immunology, Division of Host-Parasite Interaction, Institute of Medical Science, University of Tokyo, Tokyo, 108-8639, Japan
SO Oncogene (2002), 21(17), 2670-2678
CODEN: ONCNES; ISSN: 0950-9232
PB Nature Publishing Group
DT Journal
LA English
AB Defects in a developmental signaling **pathway** involving the mammalian homolog of the Drosophila segment polarity gene, **patched** are assocd. with human tumors such as basal cell carcinoma, medulloblastoma and squamous cell carcinoma. Loss of heterozygosity (LOH) in some of these tumor cells suggests that **patched** functions as a tumor suppressor gene. To evaluate the biol. significance of **patched** mutations in human sporadic tumor cells, we constructed a VSV-G pseudotyped retrovirus vector carrying the wild-type **patched** gene and transduced it into two human squamous cell carcinoma (SCC) cell lines, A431 and KA, that express only mutant **patched** mRNA. When SSC cells were transduced with Ptc virus, colony forming activity in soft agar was drastically reduced and these cells recovered anchorage independent growth when Sonic **hedgehog** (Shh), the ligand of **Patched** (Ptc), was added into the soft agar culture. Expression of exogenous **patched**, however, had no effect on anchorage independent growth of Ras-transformed NIH3T3 cells or SCC cell line, NA, which expresses wild-type **patched** mRNA. Cyclopamine, a specific **inhibitor** of the Shh/Ptc/Smo signaling **pathway**, efficiently suppressed anchorage independent growth of A431 and KA cells. These results indicate that loss of **patched** function plays a major role in the acquisition of oncogenic potential in these SCCs and further that Ptc virus would be an effective reagent for suppressing tumorigenicity of such SCCs.
RE.CNT 62 THERE ARE 62 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 8 OF 30 CAPLUS COPYRIGHT 2003 ACS
AN 2002:88212 CAPLUS
DN 136:277013
TI Expression of .DELTA.NLef1 in mouse epidermis results in differentiation of hair follicles into squamous epidermal cysts and formation of skin tumours
AU Niemann, Catherin; Owens, David M.; Hulsken, Jorg; Birchmeier, Walter; Watt, Fiona M.
CS Imperial Cancer Research Fund, London, WC2A 3PX, UK
SO Development (Cambridge, United Kingdom) (2002), 129(1), 95-109
CODEN: DEVPED; ISSN: 0950-1991
PB Company of Biologists Ltd.
DT Journal
LA English
AB To examine the consequences of repressing .beta.-catenin/Lef1 signaling in mouse epidermis, we expressed a .DELTA.NLef1 transgene, which lacks the .beta.-catenin binding site, under the control of the keratin 14 promoter. No skin abnormalities were detected before the first postnatal hair cycle. However, from 6 wk of age, mice underwent progressive hair loss which correlated with the development of dermal cysts. The cysts were derived from the base of the hair follicles and expressed morphol. and mol. markers of interfollicular epidermis. Adult mice developed spontaneous skin tumors, most of which exhibited sebaceous differentiation, which could be indicative of an origin in the upper part of the hair follicle. The transgene continued to be expressed in the tumors and .beta.-catenin signaling was still **inhibited**, as evidenced by absence of cyclin D1 expression. However, **patched** mRNA expression was upregulated, suggesting that the sonic **hedgehog pathway** might play a role in tumor formation. Based on our results and previous data on the consequences of activating .beta.-catenin/Lef1 signaling in postnatal keratinocytes, we conclude that the level of .beta.-catenin signaling dets. whether keratinocytes differentiate into hair or interfollicular epidermis, and that perturbation of the **pathway** by overexpression of .DELTA.NLef1 can lead to skin tumor formation.
RE.CNT 71 THERE ARE 71 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 9 OF 30 CAPLUS COPYRIGHT 2003 ACS
AN 2001:936904 CAPLUS
DN 136:180865
TI Dpp and Hh signaling in the Drosophila embryonic eye field
AU Chang, Ting; Mazotta, Julie; Dumstrei, Karin; Dumitrescu, Andra; Hartenstein, Volker
CS Department of Molecular Cell and Developmental Biology, University of California Los Angeles, Los Angeles, CA, 90095, USA
SO Development (Cambridge, United Kingdom) (2001), 128(23), 4691-4704
CODEN: DEVPED; ISSN: 0950-1991
PB Company of Biologists Ltd.
DT Journal
LA English
AB The authors have analyzed the function of the Decapentaplegic (Dpp) and **Hedgehog** (Hh) signaling **pathways** in partitioning the dorsal head neuroectoderm of the Drosophila embryo. This region, referred to as the anterior brain/eye anlage, gives rise to both the visual system and the protocerebrum. The anlage splits up into three main domains: the head midline ectoderm, protocerebral neuroectoderm and visual primordium. Similar to their vertebrate counterparts, Hh and Dpp play an important role in the partitioning of the anterior brain/eye anlage, Dpp is secreted in the dorsal midline of the head. Lowering Dpp levels (in dpp heterozygotes or hypomorphic alleles) results in a "cyclops" phenotype, where mid-dorsal head epidermis is transformed into dorsolateral structures, i.e., eye/optic lobe tissue, which causes a continuous visual primordium across the dorsal midline. Absence of Dpp results in the transformation of both dorsomedial and dorsolateral structures into brain neuroblasts. Regulatory genes that are required for eye/optic lobe fate, including sine oculis (so) and eyes absent (eya), are turned on in their resp. domains by Dpp. The gene zerknuellt (zen), which is expressed in response to peak levels of Dpp in the dorsal midline, secondarily represses so and eya in the dorsomedial domain. Hh and its receptor/ **inhibitor, Patched** (Ptc), are expressed in a transverse stripe along the posterior boundary of the eye field. As reported previously, Hh triggers the expression of determinants for larval eye (atonal) and adult eye (eyeless) in those cells of the eye field that are close to the Hh source. Eya and So, which are induced by Dpp, are epistatic to the Hh signal. Loss of Ptc, as well as overexpression of Hh, results in the ectopic induction of larval eye tissue in the dorsal midline (cyclopia). The authors discuss the similarities between vertebrate systems and Drosophila with regard to the fate map of the anterior brain/eye anlage, and its partitioning by Dpp and Hh signaling.
RE.CNT 81 THERE ARE 81 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 10 OF 30 CAPLUS COPYRIGHT 2003 ACS
AN 2001:783425 CAPLUS
DN 136:304999
TI The fused protein kinase regulates hedgehog-stimulated transcriptional activation in Drosophila Schneider 2 cells
AU Fukumoto, Takahiro; Watanabe-Fukunaga, Rie; Fujisawa, Kyoko; Nagata, Shigekazu; Fukunaga, Rikiro
CS Department of Genetics, B-3, Osaka University Medical School, Japan Science and Technology Corporation, Suita, 565-0871, Japan
SO Journal of Biological Chemistry (2001), 276(42), 38441-38448
CODEN: JBCHA3; ISSN: 0021-9258
PB American Society for Biochemistry and Molecular Biology
DT Journal
LA English
AB The Drosophila segment polarity gene fused encodes a putative protein-serine/threonine kinase, and plays a crit. role in the signal transduction for **Hedgehog** (Hh)-dependent gene expression. We show that the Drosophila Schneider 2 (S2) cell line has the potential to transduce the Hh-triggered intracellular signals, leading to the activation of target gene expression, when a transcription factor, Cubitus interruptus (Ci), is provided exogenously. Using S2 cells transfected with the Ci-expressing plasmid and a **patched** promoter reporter construct, we demonstrate that the forced expression of Fused (Fu) stimulates Hh-triggered and Ci-dependent transcriptional activation. The N-terminal kinase domain of Fu is required for this activity, but the C-terminal domain is not. Two kinase-inactive Fu mutants fail to enhance the reporter activation, indicating that the kinase catalytic activity is essential for this function. Neg. components of the Hh-signaling **pathway**, Costal-2 and Suppressor of Fused, strongly antagonize the Fu activity, irresp. of the presence or absence of the Fu C-terminal domain, suggesting an indirect mechanism for the **inhibition** of Fu by these proteins. Furthermore, mutational analyses of threonine 158 and serine 159, in the activation segment of the Fu protein kinase, indicate that threonine 158 is essential for Fu activity and that phosphorylation of this threonine residue may be involved in the activation of the kinase catalytic activity upon Hh stimulation.
RE.CNT 53 THERE ARE 53 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 11 OF 30 CAPLUS COPYRIGHT 2003 ACS
AN 2001:650339 CAPLUS
DN 135:327632
TI Regulation of chondrocyte terminal differentiation in the postembryonic growth plate: the role of the PTHrP-Indian hedgehog axis
AU Farquharson, Colin; Jefferies, David; Seawright, Elaine; Houston, Brian
CS Bone Biology Group, Division of Integrative Biology, Roslin Institute, Roslin, EH25 9PS, UK
SO Endocrinology (2001), 142(9), 4131-4140
CODEN: ENDOAO; ISSN: 0013-7227
PB Endocrine Society
DT Journal
LA English
AB Chondrocyte differentiation during embryonic bone growth is controlled by interactions between PTHrP and Indian **hedgehog**. The authors have now detd. that the major components of this signaling **pathway** are present in the postembryonic growth plate. PTHrP was immunolocalized throughout the growth plate, and semiquant. RT-PCR anal. of maturationally distinct chondrocyte fractions indicated that PTHrP, Indian **hedgehog**, and the PTH/PTHrP receptor were expressed at similar levels throughout the growth plate. However, **patched**, the **hedgehog** receptor, was more highly expressed in proliferating chondrocytes. Although all fractionated cells responded to PTHrP in culture by increasing thymidine incorporation and cAMP prodn. and decreasing alk. phosphatase activity, the magnitude of response was greatest in the proliferative chondrocytes. Bone morphogenetic proteins are considered likely intermediates in PTHrP signaling. Expression of bone morphogenetic protein-2 and 4-7 was detected within the growth plate, and PTHrP **inhibited** the expression of bone morphogenetic protein-4 and 6. Although organ culture studies indicated a possible paracrine role for epiphyseal chondrocyte-derived PTHrP in regulating growth plate chondrocyte differentiation, the presence within the postembryonic growth plate of functional components of the PTHrP-Indian **hedgehog pathway** suggests that local mechanisms intrinsic to the growth plate exist to control the rate of endochondral ossification.
RE.CNT 49 THERE ARE 49 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 12 OF 30 CAPLUS COPYRIGHT 2003 ACS
AN 2001:590814 CAPLUS
DN 135:301887
TI A role of PDGFR.alpha. in basal cell carcinoma proliferation
AU Xie, Jingwu; Aszterbaum, Michelle; Zhang, Xiaoli; Bonifas, Jeannette M.; Zachary, Christopher; Epstein, Ervin; McCormick, Frank
CS Cancer Research Institute, University of California, San Francisco, CA, 94115, USA
SO Proceedings of the National Academy of Sciences of the United States of America (2001), 98(16), 9255-9259
CODEN: PNASA6; ISSN: 0027-8424
PB National Academy of Sciences
DT Journal
LA English
AB Activation of the **hedgehog pathway**, through the loss of **patched** (PTC) or the activation of smoothened (SMO), occurs frequently in basal cell carcinoma (BCC), the most common human cancer. However, the mol. basis of this neoplastic effect is not understood. The downstream mol. Gli1 is known to mediate the biol. effect of the **pathway** and is itself up-regulated in all BCCs. Gli1 can drive the prodn. of BCCs in the mouse when overexpressed in the epidermis. Here we show that Gli1 can activate platelet-derived growth factor receptor .alpha. (PDGFR.alpha.) in C3H10T1/2 cells. Functional up-regulation of PDGFR.alpha. by Gli1 is accompanied by activation of the ras-ERK **pathway**, a **pathway** assocd. with cell proliferation. The relevance of this mechanism in vivo is supported by a high level expression of PDGFR.alpha. in BCCs of mice and humans. In the murine BCC cell line ASZ001, in which both copies of the PTC gene are inactivated, DNA synthesis and cell proliferation can be slowed by re-expression of PTC, which down-regulates PDGFR.alpha. expression, or by downstream **inhibition** of PDGFR.alpha. with neutralizing antibodies. Therefore, we conclude that increased expression of PDGFR.alpha. may be an important mechanism by which mutations in the **hedgehog pathway** cause BCCs.
RE.CNT 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 13 OF 30 CAPLUS COPYRIGHT 2003 ACS
AN 2001:418055 CAPLUS
DN 135:135104
TI Indian hedgehog activates hematopoiesis and vasculogenesis and can respecify prospective neurectodermal cell fate in the mouse embryo
AU Dyer, Michael A.; Farrington, Sarah M.; Mohn, Deanna; Munday, James R.; Baron, Margaret H.
CS Department of Medicine, Mount Sinai School of Medicine, New York, NY, 10029, USA
SO Development (Cambridge, United Kingdom) (2001), 128(10), 1717-1730
CODEN: DEVPED; ISSN: 0950-1991
PB Company of Biologists Ltd.
DT Journal
LA English
AB During gastrulation in the mouse, mesoderm is induced and patterned by secreted signaling mols., giving rise first to primitive erythroblasts and vascular endothelial cells. We have demonstrated previously that development of these lineages requires a signal(s) secreted from the adjacent primitive endoderm. We now show that Indian **hedgehog** (Ihh) is a primitive endoderm-secreted signal that alone is sufficient to induce formation of hematopoietic and endothelial cells. Strikingly, as seen with primitive endoderm, Ihh can respecify prospective neural ectoderm (anterior epiblast) along hematopoietic and endothelial (posterior) lineages. Downstream targets of the **hedgehog** signaling **pathway** (the genes encoding **patched**, smoothened and Gli1) are upregulated in anterior epiblasts cultured in the presence of Ihh protein, as is Bmp4, which may mediate the effects of Ihh. Blocking Ihh function in primitive endoderm **inhibits** activation of hematopoiesis and vasculogenesis in the adjacent epiblast, suggesting that Ihh is an endogenous signal that plays a key role in the development of the earliest hemato-vascular system. To our knowledge, these are the earliest functions for a **hedgehog** protein in post-implantation development in the mouse embryo.
RE.CNT 61 THERE ARE 61 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 14 OF 30 CAPLUS COPYRIGHT 2003 ACS
AN 2001:333495 CAPLUS
DN 136:64943
TI Mutations in the sterol-sensing domain of Patched suggest a role for vesicular trafficking in Smoothened regulation
AU Strutt, H.; Thomas, C.; Nakano, Y.; Stark, D.; Neave, B.; Taylor, A. M.; Ingham, P. W.
CS Department of Biomedical Science, Centre for Developmental Genetics, MRC Intercellular Signalling Group, University of Sheffield, Sheffield, UK
SO Current Biology (2001), 11(8), 608-613
CODEN: CUBLE2; ISSN: 0960-9822
PB Cell Press
DT Journal
LA English
AB The tumor suppressor gene **patched** (ptc) encodes an approx. 140 kDa polytopic transmembrane protein that binds members of the **Hedgehog** (Hh) family of signaling proteins and regulates the activity of Smoothened (Smo), a G protein-coupled receptor-like protein essential for Hh signal transduction. Ptc contains a sterol-sensing domain (SSD), a motif found in proteins implicated in the intracellular trafficking of cholesterol, and/or other cargoes. Cholesterol plays a crit. role in **Hedgehog** (Hh) signaling by facilitating the regulated secretion and sequestration of the Hh protein, to which it is covalently coupled. In addn., cholesterol synthesis **inhibitors** block the ability of cells to respond to Hh, and this finding points to an addnl. requirement for the lipid in regulating downstream components of the Hh signaling **pathway**. Although the SSD of Ptc has been linked to both the sequestration of, and the cellular response to Hh, definitive evidence for its function has so far been lacking. Here we describe the identification and characterization of two missense mutations in the SSD of Drosophila Ptc; strikingly, while both mutations abolish Smo repression, neither affects the ability of Ptc to interact with Hh. We speculate that Ptc may control Smo activity by regulating an intracellular trafficking process dependent upon the integrity of the SSD.
RE.CNT 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 15 OF 30 CAPLUS COPYRIGHT 2003 ACS
AN 2001:183615 CAPLUS
DN 134:293357
TI The CREB family of activators is required for endochondral bone development
AU Long, Fanxin; Schipani, Ernestina; Asahara, Hiroshi; Kronenberg, Henry; Montminy, Marc
CS Peptide Biology Laboratories, The Salk Institute for Biological Studies, La Jolla, CA, 92037, USA
SO Development (Cambridge, United Kingdom) (2001), 128(4), 541-550
CODEN: DEVPED; ISSN: 0950-1991
PB Company of Biologists Ltd.
DT Journal
LA English
AB We have evaluated the importance of the CREB family of transcriptional activators for endochondral bone formation by expressing a potent dominant neg. CREB **inhibitor** (A-CREB) in growth plate chondrocytes of transgenic mice. A-CREB transgenic mice exhibited short-limbed dwarfism and died minutes after birth, apparently due to respiratory failure from a diminished rib cage circumference. Consistent with the robust Ser133 phosphorylation and, hence, activation of CREB in chondrocytes within the proliferative zone of wild-type cartilage during development, chondrocytes in A-CREB mutant cartilage exhibited a profound decrease in proliferative index and a delay in hypertrophy. Correspondingly, the expression of certain signaling mols. in cartilage, most notably the Indian **hedgehog** (Ihh) receptor **patched** (Ptch), was lower in A-CREB expressing vs. wild-type chondrocytes. CREB appears to promote Ptch expression in proliferating chondrocytes via an Ihh-independent **pathway**; phospho-CREB levels were comparable in cartilage from Ihh-/- and wild-type mice. These results demonstrate the presence of a distinct signaling **pathway** in developing bone that potentiates Ihh signaling and regulates chondrocyte proliferation, at least in part, via the CREB family of activators.
RE.CNT 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 16 OF 30 CAPLUS COPYRIGHT 2003 ACS
AN 2000:880985 CAPLUS
DN 134:37058
TI Therapeutic use of an inhibitor of a hedgehog or a hedgehog-related signaling pathway
IN Lamb, Jonathan Robert; Hoyne, Gerard Francis; Dallman, Margaret Jane
PA Lorantis Limited, UK
SO PCT Int. Appl., 78 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2000074706	A1	20001214	WO 2000-GB2191	20000605
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	EP 1183040	A1	20020306	EP 2000-935413	20000605
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
	JP 2003501395	T2	20030114	JP 2001-501240	20000605
	US 2002192216	A1	20021219	US 2001-13310	20011207
PRAI	GB 1999-13350	A	19990608		
	GB 1999-21953	A	19990916		
	WO 2000-GB2191	W	20000605		

AB Use of an inhibitor of a Hedgehog signaling pathway, or an inhibitor of a pathway which is a target of the Hedgehog signaling pathway in the prepn. of a medicament for treatment of epithelial cell hyperplasia, fibrosis of tissue, inflammation, cancer or an immune disorder. Also a transgenic animal or cell line capable of expressing a component or an inhibitor of a hedgehog signaling pathway or a target pathway of the hedgehog signaling pathway.
RE.CNT 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 17 OF 30 CAPLUS COPYRIGHT 2003 ACS
AN 2000:800814 CAPLUS
DN 134:306079
TI Patched represses the Hedgehog signalling pathway by promoting modification of the Smoothened protein
AU Ingham, P. W.; Nystedt, S.; Nakano, Y.; Brown, W.; Stark, D.; Van den Heuvel, M.; Taylor, A. M.
CS MRC Intercellular Signalling Group, Centre for Developmental Genetics, University of Sheffield, UK
SO Current Biology (2000), 10(20), 1315-1318
CODEN: CUBLE2; ISSN: 0960-9822
PB Elsevier Science Ltd.
DT Journal
LA English
AB **Hedgehog** (Hh) signalling plays a central role in many developmental processes in both vertebrates and invertebrates [1]. The multipass membrane-spanning proteins **Patched** (Ptc) [2-4] and Smoothened (Smo) [5-7] have been proposed to act as subunits of a putative Hh receptor complex. According to this view, Smo functions as the transducing subunit, the activity of which is blocked by a direct interaction with the ligand-binding subunit, Ptc [8]. Activation of the intracellular signalling **pathway** occurs when Hh binds to Ptc [8-11], an event assumed to release Smo from Ptc-mediated **inhibition**. Evidence for a phys. interaction between Smo and Ptc is so far limited to studies of the vertebrate versions of these proteins when overexpressed in tissue culture systems [8, 12]. To test this model, we have overexpressed the Drosophila Smo protein in vivo and found that increasing the levels of Smo protein per se was not sufficient for activation of the **pathway**. Immunohistochem. staining of wild-type and transgenic embryos revealed distinct patterns of Smo distribution, depending on which region of the protein was detected by the antibody. Our findings suggest that Smo is modified to yield a non-functional form and this modification is promoted by Ptc in a nonstoichiometric manner.
RE.CNT 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 18 OF 30 CAPLUS COPYRIGHT 2003 ACS
AN 2000:637045 CAPLUS
DN 133:344307
TI Effects of oncogenic mutations in Smoothened and Patched can be reversed by cyclopamine
AU Taipale, Jussl; Chen, James K.; Cooper, Michael K.; Wang, Baolin; Mann, Randall K.; Milenkovic, Ljiljana; Scotts, Matthew P.; Beachy, Philip A.
CS Department of Molecular Biology and Genetics, The Johns Hopkins University School of Medicine, Baltimore, MD, 21205, USA
SO Nature (London) (2000), 406(6799), 1005-1009
CODEN: NATUAS; ISSN: 0028-0836
PB Nature Publishing Group
DT Journal
LA English
AB Basal cell carcinoma, medulloblastoma, rhabdomyosarcoma and other human tumors are assocd. with mutations that activate the proto-oncogene Smoothened (SMO) or that inactivate the tumor suppressor **Patched** (PTCH). Smoothened and **Patched** mediate the cellular response to the **Hedgehog** (Hh) secreted protein signal, and oncogenic mutations affecting these proteins cause excess activity of the Hh response **pathway**. Here we show that the plant-derived teratogen cyclopamine, which **inhibits** the Hh response, is a potential 'mechanism-based' therapeutic agent for treatment of these tumors. We show that cyclopamine or synthetic derivs. with improved potency block activation of the Hh response **pathway** and abnormal cell growth assocd. with both types of oncogenic mutation. Our results also indicate that cyclopamine may act by influencing the balance between active and inactive forms of Smoothened.
RE.CNT 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 19 OF 30 CAPLUS COPYRIGHT 2003 ACS
AN 2000:534041 CAPLUS
DN 133:306450
TI Cyclopamine Inhibition of Sonic Hedgehog Signal Transduction Is Not Mediated through Effects on Cholesterol Transport
AU Incardona, John P.; Gaffield, William; Lange, Yvonne; Cooney, Adele; Pentchev, Peter G.; Liu, Sharon; Watson, John A.; Kapur, Raj P.; Roelink, Henk
CS Department of Biological Structure, Cent. Dev. Biol., University of Washington, Seattle, WA, 98195, USA
SO Developmental Biology (2000), 224(2), 440-452
CODEN: DEBIAO; ISSN: 0012-1606
PB Academic Press
DT Journal
LA English
AB Cyclopamine is a teratogenic steroidal alkaloid that causes cyclopia by blocking Sonic **hedgehog** (Shh) signal transduction. We have tested whether this activity of cyclopamine is related to disruption of cellular cholesterol transport and putative secondary effects on the Shh receptor, **Patched** (Ptc). First, we report that the potent antagonism of Shh signaling by cyclopamine is not a general property of steroidal alkaloids with similar structure. The structural features of steroidal alkaloids previously assocd. with the induction of holoprosencephaly in whole animals are also assocd. with **inhibition** of Shh signaling in vitro. Second, by comparing the effects of cyclopamine on Shh signaling with those of compds. known to block cholesterol transport, we show that the action of cyclopamine cannot be explained by **inhibition** of intracellular cholesterol transport. However, compds. that block cholesterol transport by affecting the vesicular trafficking of the Niemann-Pick C1 protein (NPC1), which is structurally similar to Ptc, are weak Shh antagonists. Rather than supporting a direct link between cholesterol homeostasis and Shh signaling, our findings suggest that the functions of both NPC1 and Ptc involve a common vesicular transport **pathway**. Consistent with this model, we find that Ptc and NPC1 colocalize extensively in a vesicular compartment in cotransfected cells. (c) 2000 Academic Press.
RE.CNT 77 THERE ARE 77 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 20 OF 30 CAPLUS COPYRIGHT 2003 ACS
AN 2000:348738 CAPLUS
DN 133:87151
TI Conditional disruption of hedgehog signaling pathway defines its critical role in hair development and regeneration
AU Wang, Li Chun; Liu, Zhong-Ying; Gambardella, Laure; Delacour, Alexandra; Shapiro, Renee; Yang, Jianliang; Sizing, Irene; Rayhorn, Paul; Garber, Ellen A.; Benjamin, Chris D.; Williams, Kevin P.; Taylor, Frederick R.; Barrandon, Yann; Ling, Leona; Burkly, Linda C.
CS Biogen Inc, Cambridge, MA, 02142, USA
SO Journal of Investigative Dermatology (2000), 114(5), 901-908
CODEN: JIDEAE; ISSN: 0022-202X
PB Blackwell Science, Inc.
DT Journal
LA English
AB Members of the vertebrate **hedgehog** family (Sonic, Indian, and Desert) have been shown to be essential for the development of various organ systems, including neural, somite, limb, skeletal, and for male gonad morphogenesis. Sonic **hedgehog** and its cognate receptor **Patched** are expressed in the epithelial and/or mesenchymal cell components of the hair follicle. Recent studies have demonstrated an essential role for this **pathway** in hair development in the skin of Sonic **hedgehog** null embryos. We have further explored the role of the **hedgehog pathway** using anti-**hedgehog** blocking monoclonal antibodies to treat pregnant mice at different stages of gestation and have generated viable offspring that lack body coat hair. Histol. anal. revealed the presence of ectodermal placode and primodium of dermal papilla in these mice, yet the subsequent hair shaft formation was **inhibited**. In contrast, the vibrissae (whisker) development appears to be unaffected upon anti-**hedgehog** blocking monoclonal antibody treatment. Strikingly, **inhibition** of body coat hair morphogenesis also was obsd. in mice treated postnatally with anti-**hedgehog** monoclonal antibody during the growing (anagen) phase of the hair cycle. The hairless phenotype was reversible upon suspension of monoclonal antibody treatment. Taken together, our results underscore a direct role of the Sonic **hedgehog** signaling **pathway** in embryonic hair follicle development as well as in subsequent hair cycles in young and adult mice. Our system of generating an inducible and reversible hairless phenotype by anti-**hedgehog** monoclonal antibody treatment will be valuable for studying the regulation and mechanism of hair regeneration.
RE.CNT 53 THERE ARE 53 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 21 OF 30 CAPLUS COPYRIGHT 2003 ACS
AN 2000:142312 CAPLUS
DN 132:345662
TI The molecular basis of lung morphogenesis
AU Warburton, D.; Schwarz, M.; Tefft, D.; Flores-Delgado, G.; Anderson, K. D.; Cardoso, W. V.
CS Developmental Biology Program, Department of Surgery, University of Southern California Keck School of Medicine and School of Dentistry, Los Angeles, CA, USA
SO Mechanisms of Development (2000), 92(1), 55-81
CODEN: MEDVE6; ISSN: 0925-4773
PB Elsevier Science Ireland Ltd.
DT Journal; General Review
LA English
AB A review, with .apprx.250 refs. To form a diffusible interface large enough to conduct respiratory gas exchange with the circulation, the lung endoderm undergoes extensive branching morphogenesis and alveolization, coupled with angiogenesis and vasculogenesis. It is becoming clear that many of the key factors detg. the process of branching morphogenesis, particularly of the respiratory organs, are highly conserved through evolution. Synthesis of information from null mutations in Drosophila and mouse indicates that members of the sonic **hedgehog/patched**/smoothened/Gli/FGF/FGFR/sprouty **pathway** are functionally conserved and extremely important in detg. respiratory organogenesis through mesenchymal-epithelial inductive signaling, which induces epithelial proliferation, chemotaxis, and organ-specific gene expression. Transcriptional factors including Nkx2.1, HNF family forkhead homologs, GATA family zinc finger factors, pou and hox, helix-loop-helix (HLH) factors, Id factors, glucocorticoid and retinoic acid receptors mediate and integrate the developmental genetic instruction of lung morphogenesis and cell lineage detn. Signaling by the IGF, EGF, and TGF-.beta./BMP **pathways**, extracellular matrix components and integrin signaling **pathways** also directs lung morphogenesis as well as proximo-distal lung epithelial cell lineage differentiation. Sol. factors secreted by lung mesenchyme comprise a complete inducer of lung morphogenesis. In general, peptide growth factors signaling through cognate receptors with tyrosine kinase intracellular signaling domains such as FGFR, EGFR, IGFR, PDGFR, and c-met stimulate lung morphogenesis. On the other hand, cognate receptors with serine/threonine kinase intracellular signaling domains, such as the TGF-.beta. receptor family are **inhibitory**, although BMP4 and BMPR also play key inductive roles. Pulmonary neuroendocrine cells differentiate earliest in gestation from among multipotential lung epithelial cells. MASH1 null mutant mice do not develop PNE cells. Proximal and distal airway epithelial phenotypes differentiate under distinct transcriptional control mechanisms. It is becoming clear that angiogenesis and vasculogenesis of the pulmonary circulation and capillary network are closely linked with and may be necessary for lung epithelial morphogenesis. Like epithelial morphogenesis, pulmonary vascularization is subject to a fine balance between pos. and neg. factors. Angiogenic and vasculogenic factors include VEGF, which signals through cognate receptors flk and flt, while novel anti-angiogenic factors include EMAP II.
RE.CNT 258 THERE ARE 258 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 22 OF 30 CAPLUS COPYRIGHT 2003 ACS
AN 1999:672583 CAPLUS
DN 131:267077
TI Use of steroidal alkaloid derivatives as inhibitors of hedgehog signaling pathways
IN Beachy, Philip A.; Cooper, Michael K.; Porter, Jeffrey A.
PA Johns Hopkins University School of Medicine, USA
SO PCT Int. Appl., 136 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9952534	A1	19991021	WO 1999-US7811	19990409
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	US 2002006931	A1	20020117	US 1998-90622	19980604
	US 6432970	B2	20020813		
	CA 2326654	AA	19991021	CA 1999-2326654	19990409
	AU 9934860	A1	19991101	AU 1999-34860	19990409
	EP 1067939	A1	20010117	EP 1999-916563	19990409
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
	JP 2002511415	T2	20020416	JP 2000-543144	19990409
PRAI	US 1998-81186P	P	19980409		
	US 1998-81263P	P	19980409		
	US 1998-90622	A	19980604		
	WO 1999-US7811	W	19990409		

OS MARPAT 131:267077
AB The present invention makes available assays and reagents inhibiting paracrine and/or autocrine signals produced by a hedgehog protein or aberrant activation of a hedgehog signal transduction pathway, e.g., which involve the use of a steroidal alkaloid or other small mol.
RE.CNT 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 23 OF 30 CAPLUS COPYRIGHT 2003 ACS
AN 1999:594300 CAPLUS
DN 131:309211
TI Mammalian suppressor-of-fused modulates nuclear-cytoplasmic shuttling of GLI-1
AU Kogerman, Priit; Grimm, Thomas; Kogerman, Lembi; Krause, Darren; Unden, Anne Birgitte; Sandstedt, Bengt; Toftgard, Rune; Zaphiropoulos, Peter G.
CS Department of Biosciences, Karolinska Institutet, Huddinge, S-14157, Swed.
SO Nature Cell Biology (1999), 1(5), 312-319
CODEN: NCBIFN; ISSN: 1465-7392
PB Macmillan Magazines Ltd
DT Journal
LA English
AB Sonic **hedgehog**, **Patched** and Gli are components of a mammalian signaling **pathway** that has been conserved during evolution and which has a central role in the control of pattern formation and cellular proliferation during development. Here the authors identify the human Suppressor-of-Fused (SUFUH) complementary DNA and show that the gene product interacts phys. with the transcriptional effector GLI-1, can sequester GLI-1 in the cytoplasm, but can also interact with GLI-1 on DNA. Functionally, SUFUH **inhibits** transcriptional activation by GLI-1, as well as osteogenic differentiation in response to signaling from Sonic **hedgehog**. Localization of GLI-1 is influenced by the presence of a nuclear-export signal, and GLI-1 becomes constitutively nuclear when this signal is mutated or nuclear export is **inhibited**. These results show that SUFUH is a conserved neg. regulator of GLI-1 signaling that may affect nuclear-cytoplasmic shuttling of GLI-1 or the activity of GLI-1 in the nucleus and thereby modulate cellular responses.
RE.CNT 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 24 OF 30 CAPLUS COPYRIGHT 2003 ACS
AN 1999:529175 CAPLUS
DN 131:141473
TI A transcription factor regulating the hedgehog-mediated signaling pathway that is controlled by phosphorylation and dephosphorylation
IN Beachy, Phillip A.; Tsai, Ming-jer; Tsai, Sophia Y.; Krishnan, Venkatesh; Chen, Chien-huan
PA The Johns Hopkins University School of Medicine, USA; Baylor College of Medicine
SO PCT Int. Appl., 76 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9941281	A1	19990819	WO 1999-US3112	19990211
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 6277566	B1	20010821	US 1998-23249	19980213
AU 9926767	A1	19990830	AU 1999-26767	19990211
US 2002102646	A1	20020801	US 2001-934035	20010821
PRAI US 1998-23249	A	19980213		
WO 1999-US3112	W	19990211		

AB A transcription factor involved in regulation of the **hedgehog** signaling **pathway** and that binds sonic **hedgehog** response elements upon **hedgehog**-mediated dephosphorylation is described. **Hedgehog** response elements (HRE) that interact with the dephosphorylated transcription factors are also provided as well as methods for identifying compds. that are phosphatase **inhibitors**. Methods of treating tumors in a subject by modulating the phosphorylation of the transcription factor are also included. **Hedgehog** protein was found to increase the level of the Ci (Cubitus Interruptus) transcription factor before transcription of the gene was detectable, indicating some form of protein/protein interaction and modification of the transcription factor. **Hedgehog** also increased the transcription of the **patched** gene. Mutation of **hedgehog** response elements in the **patched** gene promoter lowered levels of expression of a reporter. Expts. with phosphatases and phosphatase **inhibitors** showed that phosphorylation and dephosphorylation played a role in the modification of Ci with **hedgehog** inducing dephosphorylation. Dephosphorylation resulted in Ci moving from the cytoplasm to the nucleus.

RE.CNT 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 25 OF 30 CAPLUS COPYRIGHT 2003 ACS
AN 1999:475175 CAPLUS
DN 131:252202
TI The zinc finger protein GLI induces cellular sensitivity to the mTOR inhibitor rapamycin
AU Louro, Iuri D.; McKie-Bell, Peggy; Gosnell, Helen; Brindley, Bianca C.; Bucy, R. Patrick; Ruppert, J. Michael
CS Department of Biochemistry and Molecular Genetics, University of Alabama at Birmingham, Birmingham, AL, 35294-3300, USA
SO Cell Growth & Differentiation (1999), 10(7), 503-516
CODEN: CGDIE7; ISSN: 1044-9523
PB American Association for Cancer Research
DT Journal
LA English
AB The protein synthetic machinery is activated by diverse genetic alterations during tumor progression in vivo and represents an attractive target for cancer therapy. We show that rapamycin **inhibits** the induction of transformed foci in vitro by GLI, a transcription factor that functions in the sonic **hedgehog-patched pathway** in tumors. In control cells, which were nontransformed epithelioid RK3E cells and deriv. c-MYC- or RAS- transformed sister cell lines, rapamycin **inhibits** mTOR and mTOR-dependent activities but increases global protein synthesis, perhaps by activating a feedback mechanism. In GLI-transformed cells, rapamycin **inhibits** global protein synthesis and turnover and prevents cellular proliferation. In contrast to its effects on protein synthesis, rapamycin affects bromodeoxyuridine incorporation and cell cycle occupancy of GLI cells and control cells to a similar extent. Rare, variant GLI cells isolated by selection in rapamycin are also drug-resistant for protein metab. and for cell cycle progression through G1. Our results indicate that sensitivity to rapamycin can be induced by a specific oncogene and that **inhibition** of global protein metab. is linked to the rapamycin-sensitive phenotype.
RE.CNT 95 THERE ARE 95 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 26 OF 30 CAPLUS COPYRIGHT 2003 ACS
AN 1999:106072 CAPLUS
DN 130:249940
TI Sonic hedgehog signaling by the Patched-Smoothened receptor complex
AU Murone, Maximilien; Rosenthal, Arnon; de Sauvage, Frederic J.
CS Department of Molecular Oncology, Genentech Inc., South San Francisco, CA, 94080, USA
SO Current Biology (1999), 9(2), 76-84
CODEN: CUBLE2; ISSN: 0960-9822
PB Current Biology Publications
DT Journal
LA English
AB The **Hedgehog** (Hh) family of secreted proteins is involved in a no. of developmental processes as well as in cancer. Genetic and biochem. data suggest that the Sonic **hedgehog** (Shh) receptor is composed of at least two proteins: the tumor suppressor protein **Patched** (Ptc) and the seven-transmembrane protein Smoothened (Smo). Using a biochem. assay for activation of the transcription factor Gli, a downstream component of the Hh **pathway**, we show here that Smo functions as the signaling component of the Shh receptor, and that this activity can be blocked by Ptc. The **inhibition** of Smo by Ptc can be relieved by the addn. of Shh. Furthermore, oncogenic forms of Smo are insensitive to Ptc repression in this assay. Mapping of the Smo domains required for binding to Ptc and for signaling revealed that the Smo-Ptc interaction involves mainly the amino terminus of Smo, and that the third intracellular loop and the seventh transmembrane domain are required for signaling. In conclusion, these data demonstrate that Smo is the signaling component of a multicomponent Hh receptor complex and that Ptc is a ligand-regulated **inhibitor** of Smo. Different domains of Smo are involved in Ptc binding and activation of a Gli reporter construct. The latter requires the third intracellular loop and the seventh transmembrane domain of Smo, regions often involved in coupling to G proteins. No changes in the levels of cAMP or calcium assocd. with such **pathways** could be detected following receptor activation, however.
RE.CNT 52 THERE ARE 52 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 27 OF 30 CAPLUS COPYRIGHT 2003 ACS
AN 1999:36456 CAPLUS
DN 130:205360
TI Repression of hedgehog signaling and BMP4 expression in growth plate cartilage by fibroblast growth factor receptor 3
AU Naski, Michael C.; Colvin, Jennifer S.; Coffin, J. Douglas; Ornitz, David M.
CS Department of Molecular Biology and Pharmacology, Washington University School of Medicine, St. Louis, MO, 63110, USA
SO Development (Cambridge, United Kingdom) (1998), 125(24), 4977-4988
CODEN: DEVPED; ISSN: 0950-1991
PB Company of Biologists Ltd.
DT Journal
LA English
AB Fibroblast growth factor receptor 3 (FGFR3) is a key regulator of skeletal growth and activating mutations in Fgfr3 cause achondroplasia, the most common genetic form of dwarfism in humans. Little is known about the mechanism by which FGFR3 **inhibits** bone growth and how FGFR3 signaling interacts with other signaling **pathways** that regulate endochondral ossification. To understand these mechanisms, we targeted the expression of an activated FGFR3 to growth plate cartilage in mice using regulatory elements from the collagen II gene. As with humans carrying the achondroplasia mutation, the resulting transgenic mice are dwarfed, with axial, appendicular and craniofacial skeletal hypoplasia. We found that FGFR3 **inhibited** endochondral bone growth by markedly **inhibiting** chondrocyte proliferation and by slowing chondrocyte differentiation. Significantly, FGFR3 downregulated the Indian **hedgehog** (Ihh) signaling **pathway** and Bmp4 expression in both growth plate chondrocytes and in the perichondrium. Conversely, Bmp4 expression is upregulated in the perichondrium of Fgfr3-/- mice. These data support a model in which Fgfr3 is an upstream neg. regulator of the **hedgehog** (Hh) signaling **pathway**. Addnl., Fgfr3 may coordinate the growth and differentiation of chondrocytes with the growth and differentiation of osteoprogenitor cells by simultaneously modulating Bmp4 and **patched** expression in both growth plate cartilage and in the perichondrium.
RE.CNT 68 THERE ARE 68 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 28 OF 30 CAPLUS COPYRIGHT 2003 ACS
AN 1998:356088 CAPLUS
DN 129:118989
TI Teratogen-mediated inhibition of target tissue response to Shh signaling
AU Cooper, Michael K.; Porter, Jeffery A.; Young, Keith E.; Beachy, Philip A.
CS Dep. Neurology and Howard Hughes Med. Inst., Dep. Molecular Biology and Genetics, Johns Hopkins Univ. Sch. Med., Baltimore, MD, 21205, USA
SO Science (Washington, D. C.) (1998), 280(5369), 1603-1607
CODEN: SCIEAS; ISSN: 0036-8075
PB American Association for the Advancement of Science
DT Journal
LA English
AB Veratrum alkaloids and distal **inhibitors** of cholesterol biosynthesis have been studied for more than 30 yr as potent teratogens capable of inducing cyclopia and other birth defects. Here, it is shown that these compds. specifically block the Sonic **hedgehog** (Shh) signaling **pathway**. These teratogens did not prevent the sterol modification of Shh during autoprocessing but rather **inhibited** the response of target tissues to Shh, possibly acting through the sterol sensing domain within the **Patched** protein regulator of Shh response.
RE.CNT 48 THERE ARE 48 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 29 OF 30 CAPLUS COPYRIGHT 2003 ACS
AN 1998:191636 CAPLUS
DN 129:14538
TI Control of somite patterning by Sonic hedgehog and its downstream signal response genes
AU Borycki, Anne-Gaelle; Mendham, Lori; Emerson, Charles P., Jr.
CS Department of Cell and Developmental Biology, University of Pennsylvania School of Medicine, Philadelphia, PA, 19104-6058, USA
SO Development (Cambridge, United Kingdom) (1998), 125(4), 777-790
CODEN: DEVPED; ISSN: 0950-1991
PB Company of Biologists Ltd.
DT Journal
LA English
AB In the avian embryo, previous work has demonstrated that the notochord provides inductive signals to activate myoD and pax1 regulatory genes, which are expressed in the dorsal and ventral somite cells that give rise to myotomal and sclerotomal lineages. Here, the authors present bead implantation and antisense **inhibition** expts. that show that Sonic **hedgehog** is both a sufficient and essential notochord signal mol. for myoD and pax1 activation in somites. Furthermore, the authors show that genes of the Sonic **hedgehog** signal response **pathway**, specifically **patched**, the Sonic **hedgehog** receptor, and gli and gli2/4, zinc-finger transcription factors, are activated in coordination with somite formation, establishing that Sonic **hedgehog** response genes play a regulatory role in coordinating the response of somites to the constitutive notochord Sonic **hedgehog** signal. Furthermore, the expression of **patched**, gli and gli2/4 is differentially patterned in the somite, providing mechanisms for differentially transducing the Sonic **hedgehog** signal to the myotomal and sclerotomal lineages. Finally, the authors show that the activation of gli2/4 is controlled by the process of somite formation and signals from the surface ectoderm, whereas upregulation of **patched** and activation of gli is controlled by the process of somite formation and a Sonic **hedgehog** signal. The Sonic **hedgehog** signal response genes, therefore, have important functions in regulating the initiation of the Sonic **hedgehog** response in newly forming somites and in regulating the patterned expression of myoD and pax1 in the myotomal and sclerotomal lineages following somite formation.
RE.CNT 76 THERE ARE 76 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 30 OF 30 CAPLUS COPYRIGHT 2003 ACS
AN 1997:522311 CAPLUS
TI Hedgehog and its patched-smoothened receptor complex. A novel signaling mechanism at the cell surface
AU Alcedo, Joy; Noll, Markus
CS Institut Molekularbiologie, Universitat Zurich, Zurich, CH-8057, Switz.
SO Biological Chemistry (1997), 378(7), 583-590
CODEN: BICHF3; ISSN: 1431-6730
PB de Gruyter
DT Journal
LA English
AB Pattern formation and morphogenesis depend on the careful execution of complex genetic programs, which are conserved in multicellular organisms. An important signal in some of these programs in Drosophila and vertebrates is the secreted **Hedgehog** (Hh) protein, which primarily functions as an inducer of morphogenetic signals. The Hh signal plays a decisive role in such crit. developmental processes as neurulation and somite and limb formation. The Hh signaling **pathway** exhibits a novel mechanism of signal reception and transduction. In the absence of the Hh signal, the membrane protein **Patched** (Ptc) represses the constitutive signaling activity of a second membrane protein, Smoothened (Smo), by virtue of its ability to form a Ptc-Smo complex. Hence, mutations within the ptc gene that result in the failure of Ptc to **inhibit** Smo lead to constitutive activity of the Hh signalling **pathway** and to cancer, such as basal cell carcinoma. For activation of Hh-target genes, the N-terminal signalling domain of Hh binds to the Ptc-Smo receptor complex to activate two parallel signalling **pathways**. Furthermore, Hh limits its own range of action by impeding its diffusion through (i) covalent linkage of its N-terminal signaling moiety to cholesterol, mediated by the cholesterol transferase activity of its C-terminal moiety, and (ii) induction of, and sequestration by, its antagonist, Ptc.

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=> s hedgehog?
L1        2883 HEDGEHOG?

=> s inhibit?
L2     1601600 INHIBIT?

=> s normal?
L3      956256 NORMAL?

=> s l1(l)l2(l)l3
L4           75 L1(L)L2(L)L3

=> d l4 1-75 bib,ab,kwic

L4   ANSWER 1 OF 75  CAPLUS  COPYRIGHT 2003 ACS on STN
AN   2003:583930  CAPLUS
TI   Hedgehog signaling: Progenitor phenotype in small-cell lung cancer
AU   Watkins, D. Neil; Berman, David M.; Baylin, Stephen B.
CS   Sidney Kimmel Comprehensive Cancer Center; Molecular Biology and Genetics,
     Johns Hopkins University School of Medicine, Baltimore, MD, USA
SO   Cell Cycle (2003), 2(3), 196-198
     CODEN: CCEYAS; ISSN: 1538-4101
PB   Landes Bioscience
DT   Journal; General Review
LA   English
AB   A review. Recently, we have shown that small cell lung cancer (SCLC) is
     dependent on activation of Hedgehog signaling, an embryonic
     pathway implicated in development, morphogenesis and the regulation of
     stem cell fates. These findings form the framework for an emerging view
     of cancer as a process of aberrant organogenesis in which progenitor/ stem
     cells escape dependence on niche signaling through mutation in genes such
     as Ptch, or through persistent activation of progenitor cell pathways.
     Interestingly, the normally quiescent airway epithelial
     compartment uses the Hh pathway to repopulate itself when challenged by
     injury. How Hh signaling works to promote the malignant phenotype
     promises to be as important biol. as the promise of Hh pathway
     inhibitors are clin.
RE.CNT  39    THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD
              ALL CITATIONS AVAILABLE IN THE RE FORMAT
AB   A review. Recently, we have shown that small cell lung cancer (SCLC) is
     dependent on activation of Hedgehog signaling, an embryonic
     pathway implicated in development, morphogenesis and the regulation of
     stem cell fates. These findings form the framework for an emerging view
     of cancer as a process of aberrant organogenesis in which progenitor/ stem
     cells escape dependence on niche signaling through mutation in genes such
     as Ptch, or through persistent activation of progenitor cell pathways.
     Interestingly, the normally quiescent airway epithelial
     compartment uses the Hh pathway to repopulate itself when challenged by
     injury. How Hh signaling works to promote the malignant phenotype
     promises to be as important biol. as the promise of Hh pathway
     inhibitors are clin.

L4   ANSWER 2 OF 75  CAPLUS  COPYRIGHT 2003 ACS on STN
AN   2003:539960  CAPLUS
TI   Wnt regulation of progenitor maturation in the cortex depends on Shh or
     fibroblast growth factor 2
AU   Viti, Jane; Gulacsi, Alexandra; Lillien, Laura
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CS Department of Neurobiology and Pittsburgh Cancer Institute, University of Pittsburgh School of Medicine, Pittsburgh, PA, 15261, USA
SO Journal of Neuroscience (2003), 23(13), 5919-5927
CODEN: JNRSDS; ISSN: 0270-6474
PB Society for Neuroscience
DT Journal
LA English
AB In the embryonic mouse cerebral cortex, progenitors in the ventricular zone (VZ) undergo a developmental change between embryonic day 13 (E13) and E15. This results in the generation of a secondary proliferative population and the appearance of a second germinal layer, the subventricular zone (SVZ). We have shown previously that bone morphogenetic proteins (BMPs) and fibroblast growth factor 2 (FGF2) act antagonistically to regulate the development of a subset of SVZ progenitors that **normally** express a high level of epidermal growth factor (EGF) receptors and divide in response to EGF. In the present study, we show that Wnt 7a, Wnt 7b, and Sonic **hedgehog** (Shh) promote progenitor maturation in explant cultures, as reported for FGF2. Wnts 7a and 7b also stimulate the proliferation of neurogenic progenitors and increase the no. of cells that can generate primary neurospheres. To det. whether Wnts, FGF2, and Shh act independently or in a common pathway, each factor was **inhibited** in cortical explants. This revealed that endogenous Wnts, FGF2, and Shh **normally** contribute to progenitor maturation. Moreover, Wnt 7a depends on FGF2 or Shh to promote maturation but not proliferation. Maturation induced by blocking BMPs also depends on Shh. In contrast, FGF2 promotes maturation by a Shh-independent mechanism. In vivo, progenitors infected with a Wnt 7a retrovirus at E10.5 were found preferentially in the SVZ at E16.5. These findings suggest that Wnts depend on Shh or FGF2 to promote progenitor maturation to an SVZ state in the embryonic cortex.
RE.CNT 48 THERE ARE 48 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT
AB In the embryonic mouse cerebral cortex, progenitors in the ventricular zone (VZ) undergo a developmental change between embryonic day 13 (E13) and E15. This results in the generation of a secondary proliferative population and the appearance of a second germinal layer, the subventricular zone (SVZ). We have shown previously that bone morphogenetic proteins (BMPs) and fibroblast growth factor 2 (FGF2) act antagonistically to regulate the development of a subset of SVZ progenitors that **normally** express a high level of epidermal growth factor (EGF) receptors and divide in response to EGF. In the present study, we show that Wnt 7a, Wnt 7b, and Sonic **hedgehog** (Shh) promote progenitor maturation in explant cultures, as reported for FGF2. Wnts 7a and 7b also stimulate the proliferation of neurogenic progenitors and increase the no. of cells that can generate primary neurospheres. To det. whether Wnts, FGF2, and Shh act independently or in a common pathway, each factor was **inhibited** in cortical explants. This revealed that endogenous Wnts, FGF2, and Shh **normally** contribute to progenitor maturation. Moreover, Wnt 7a depends on FGF2 or Shh to promote maturation but not proliferation. Maturation induced by blocking BMPs also depends on Shh. In contrast, FGF2 promotes maturation by a Shh-independent mechanism. In vivo, progenitors infected with a Wnt 7a retrovirus at E10.5 were found preferentially in the SVZ at E16.5. These findings suggest that Wnts depend on Shh or FGF2 to promote progenitor maturation to an SVZ state in the embryonic cortex.

L4 ANSWER 3 OF 75 CAPLUS COPYRIGHT 2003 ACS on STN

AN 2003:366249 CAPLUS
DN 139:131209
TI Inhibition of Epithelial Ductal Branching in the Prostate by Sonic Hedgehog Is Indirectly Mediated by Stromal Cells
AU Wang, Bu-er; Shou, Jianyong; Ross, Sarajane; Koeppen, Hartmut; de Sauvage, Frederic J.; Gao, Wei-Qiang
CS Department of Molecular Oncology, Genentech, Inc., South San Francisco, CA, 94080, USA
SO Journal of Biological Chemistry (2003), 278(20), 18506-18513
CODEN: JBCHA3; ISSN: 0021-9258
PB American Society for Biochemistry and Molecular Biology
DT Journal
LA English
AB Sonic **hedgehog** (Shh), a vertebrate homolog of the Drosophila segment-polarity gene **hedgehog**, has been reported to play an important role during **normal** development of various tissues. Abnormal activities of Shh signaling pathway have been implicated in tumorigenesis such as basal cell carcinomas and medulloblastomas. Here we show that Shh signaling neg. regulates prostatic epithelial ductal morphogenesis. In organotypic cultures of developing rat prostates, Shh **inhibited** cell proliferation and promoted differentiation of luminal epithelial cells. The expression pattern of Shh and its receptors suggests a paracrine mechanism of action. The Shh receptors Ptc1 (Patched1) and Ptc2 were found to be expressed in prostatic stromal cells adjacent to the epithelium, where Shh itself was produced. This paracrine model was confirmed by co-culturing the developing prostate in the presence of stromal cells transfected with a vector expressing a constitutively active form of Smoothened, the real effector of the Shh signaling pathway. Furthermore, expression of activin A and TGF-.beta.1 that were shown previously to **inhibit** prostatic epithelial branching was up-regulated following Shh treatment in the organotypic cultures. Taken together, these results suggest that Shh neg. regulates prostatic ductal branching indirectly by acting on the surrounding stromal cells, at least partly via up-regulating expression of activin A and TGF-.beta.1.
RE.CNT 81 THERE ARE 81 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT
AB Sonic **hedgehog** (Shh), a vertebrate homolog of the Drosophila segment-polarity gene **hedgehog**, has been reported to play an important role during **normal** development of various tissues. Abnormal activities of Shh signaling pathway have been implicated in tumorigenesis such as basal cell carcinomas and medulloblastomas. Here we show that Shh signaling neg. regulates prostatic epithelial ductal morphogenesis. In organotypic cultures of developing rat prostates, Shh **inhibited** cell proliferation and promoted differentiation of luminal epithelial cells. The expression pattern of Shh and its receptors suggests a paracrine mechanism of action. The Shh receptors Ptc1 (Patched1) and Ptc2 were found to be expressed in prostatic stromal cells adjacent to the epithelium, where Shh itself was produced. This paracrine model was confirmed by co-culturing the developing prostate in the presence of stromal cells transfected with a vector expressing a constitutively active form of Smoothened, the real effector of the Shh signaling pathway. Furthermore, expression of activin A and TGF-.beta.1 that were shown previously to **inhibit** prostatic epithelial branching was up-regulated following Shh treatment in the organotypic cultures. Taken together, these results suggest that Shh neg. regulates prostatic ductal branching indirectly by acting on the surrounding stromal cells, at least partly via up-regulating expression of activin A and TGF-.beta.1.

L4 ANSWER 4 OF 75 CAPLUS COPYRIGHT 2003 ACS on STN
AN 2003:341229 CAPLUS
DN 139:50742
TI The interplay of genetic and environmental factors in craniofacial morphogenesis: holoprosencephaly and the role of cholesterol
AU Edison, Robin; Muenke, Maximilian
CS Medical Genetics Branch, National Human Genome Research Institute, Department of Health and Human Services, National Institutes of Health, Bethesda, MD, USA
SO Congenital Anomalies (2003), 43(1), 1-21
CODEN: CGANE7; ISSN: 0914-3505
PB Japanese Teratology Society
DT Journal; General Review
LA English
AB A review. Cyclopia, the paradigmatic "face [that] predicts the brain" in severe holoprosencephaly (HPE), was recognized since ancient times. Descriptive embryologists and pathologists have noted the continuum of defective sepn. of the forebrain and loss of central nervous system (CNS) midline structures for more than a century. It was recognized more recently that **inhibitors** of cholesterol biosynthesis, whether consumed in native plants by range sheep, or exptl. applied to early embryos, could phenocopy the natural malformation, as could a variety of other teratogens (maternal diabetes, alc.). Yet it was less than a decade that the genomic knowledge base and powerful analytic methods have brought the sciences of descriptive, mol., and genetic embryol. within range of each other. In this review, the authors discuss the clin. presentations and pathogenesis of HPE. We will outline various genetic and teratogenic mechanisms leading to HPE. Lastly, the authors will attempt to examine the pivotal role of cholesterol and the Sonic **Hedgehog** (Shh) pathway in this disorder and in **normal** embryonic forebrain development. "If the brain were so simple that we could understand it, we'd be so simple, we couldn't.".
RE.CNT 156 THERE ARE 156 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT
AB A review. Cyclopia, the paradigmatic "face [that] predicts the brain" in severe holoprosencephaly (HPE), was recognized since ancient times. Descriptive embryologists and pathologists have noted the continuum of defective sepn. of the forebrain and loss of central nervous system (CNS) midline structures for more than a century. It was recognized more recently that **inhibitors** of cholesterol biosynthesis, whether consumed in native plants by range sheep, or exptl. applied to early embryos, could phenocopy the natural malformation, as could a variety of other teratogens (maternal diabetes, alc.). Yet it was less than a decade that the genomic knowledge base and powerful analytic methods have brought the sciences of descriptive, mol., and genetic embryol. within range of each other. In this review, the authors discuss the clin. presentations and pathogenesis of HPE. We will outline various genetic and teratogenic mechanisms leading to HPE. Lastly, the authors will attempt to examine the pivotal role of cholesterol and the Sonic **Hedgehog** (Shh) pathway in this disorder and in **normal** embryonic forebrain development. "If the brain were so simple that we could understand it, we'd be so simple, we couldn't.".

L4 ANSWER 5 OF 75 CAPLUS COPYRIGHT 2003 ACS on STN
AN 2003:329403 CAPLUS
DN 139:143527
TI Identification of a small molecule inhibitor of the hedgehog signaling pathway: Effects on basal cell carcinoma-like lesions

AU Williams, Juliet A.; Guicherit, Oivin M.; Zaharian, Beatrice I.; Xu, Yin; Chai, Ling; Wichterle, Hynek; Kon, Charlene; Gatchalian, Christine; Porter, Jeffery A.; Rubin, Lee L.; Wang, Frank Y.
CS Curis Incorporated, Cambridge, MA, 02138, USA
SO Proceedings of the National Academy of Sciences of the United States of America (2003), 100(8), 4616-4621
CODEN: PNASA6; ISSN: 0027-8424
PB National Academy of Sciences
DT Journal
LA English
AB The link between basal cell carcinoma (BCC) and aberrant activation of the **Hedgehog** (Hh) signaling pathway has been well established in humans and in mouse models. Here we report the development of assays, including two novel in vitro BCC models, which allowed us to screen for Hh **inhibitors** and test their validity as potential treatments for BCC. We identified a novel small mol. Hh **inhibitor** (CUR61414) that can block elevated Hh signaling activity resulting from oncogenic mutations in Patched-1. Moreover, CUR61414 can suppress proliferation and induce apoptosis of basaloid nests in the BCC model systems, whereas having no effect on **normal** skin cells. These findings directly demonstrate that the use of Hh **inhibitors** could be a valid therapeutic approach for treating BCC.
RE.CNT 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT
AB The link between basal cell carcinoma (BCC) and aberrant activation of the **Hedgehog** (Hh) signaling pathway has been well established in humans and in mouse models. Here we report the development of assays, including two novel in vitro BCC models, which allowed us to screen for Hh **inhibitors** and test their validity as potential treatments for BCC. We identified a novel small mol. Hh **inhibitor** (CUR61414) that can block elevated Hh signaling activity resulting from oncogenic mutations in Patched-1. Moreover, CUR61414 can suppress proliferation and induce apoptosis of basaloid nests in the BCC model systems, whereas having no effect on **normal** skin cells. These findings directly demonstrate that the use of Hh **inhibitors** could be a valid therapeutic approach for treating BCC.

L4 ANSWER 6 OF 75 CAPLUS COPYRIGHT 2003 ACS on STN
AN 2003:301922 CAPLUS
DN 139:81057
TI The morphogen Sonic hedgehog is an axonal chemoattractant that collaborates with Netrin-1 in midline axon guidance
AU Charron, Frederic; Stein, Elke; Jeong, Juhee; McMahon, Andrew P.; Tessier-Lavigne, Marc
CS Department of Biological Sciences Howard Hughes Medical Institute, Stanford University, Stanford, CA, 94305, USA
SO Cell (Cambridge, MA, United States) (2003), 113(1), 11-23
CODEN: CELLB5; ISSN: 0092-8674
PB Cell Press
DT Journal
LA English
AB Developing axons are guided to their targets by attractive and repulsive guidance cues. In the embryonic spinal cord, the floor plate chemoattractant Netrin-1 is required to guide commissural neuron axons to the midline. However, genetic evidence suggests that other chemoattractant(s) are also involved. We show that the morphogen Sonic **hedgehog** (Shh) can mimic the addnl. chemoattractant activity of the floor plate in vitro and can act directly as a chemoattractant on isolated axons. Cyclopamine-mediated **inhibition** of the Shh

signaling mediator Smoothened (Smo) or conditional inactivation of Smo in commissural neurons indicate that Smo activity is important for the addnl. chemoattractant activity of the floor plate in vitro and for the **normal** projection of commissural axons to the floor plate in vivo. These results provide evidence that Shh, acting via Smo, is a midline-derived chemoattractant for commissural axons and show that a morphogen can also act as an axonal chemoattractant.

RE.CNT 46 THERE ARE 46 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

AB Developing axons are guided to their targets by attractive and repulsive guidance cues. In the embryonic spinal cord, the floor plate chemoattractant Netrin-1 is required to guide commissural neuron axons to the midline. However, genetic evidence suggests that other chemoattractant(s) are also involved. We show that the morphogen Sonic **hedgehog** (Shh) can mimic the addnl. chemoattractant activity of the floor plate in vitro and can act directly as a chemoattractant on isolated axons. Cyclopamine-mediated **inhibition** of the Shh signaling mediator Smoothened (Smo) or conditional inactivation of Smo in commissural neurons indicate that Smo activity is important for the addnl. chemoattractant activity of the floor plate in vitro and for the **normal** projection of commissural axons to the floor plate in vivo. These results provide evidence that Shh, acting via Smo, is a midline-derived chemoattractant for commissural axons and show that a morphogen can also act as an axonal chemoattractant.

L4 ANSWER 7 OF 75 CAPLUS COPYRIGHT 2003 ACS on STN
AN 2003:291279 CAPLUS
DN 139:18866
TI GSK-3: Tricks of the trade for a multi-tasking kinase
AU Doble, Bradley W.; Woodgett, James R.
CS Ontario Cancer Institute, Toronto, ON, M5G 2M9, Can.
SO Journal of Cell Science (2003), 116(7), 1175-1186
CODEN: JNCSAI; ISSN: 0021-9533
PB Company of Biologists Ltd.
DT Journal; General Review
LA English

AB A review. Glycogen synthase kinase-3 (GSK-3) is a multifunctional serine/threonine kinase found in all eukaryotes. The enzyme is a key regulator of numerous signaling pathways, including cellular responses to Wnt, receptor tyrosine kinases, and G-protein-coupled receptors and is involved in a wide range of cellular processes, ranging from glycogen metab. to cell cycle regulation and proliferation. GSK-3 is unusual in that it is **normally** active in cells and is primarily regulated through **inhibition** of its activity. Another peculiarity compared with other protein kinases is its preference for primed substrates, i.e., substrates previously phosphorylated by another kinase. Several recent advances have improved the understanding of GSK-3 regulation in multiple pathways. These include the soln. of the crystal structure of GSK-3, which has provided insight into GSK-3's penchant for primed substrates and the regulation of GSK-3 by serine phosphorylation, and findings related to the involvement of GSK-3 in the Wnt/.beta.-catenin and **Hedgehog** pathways. Finally, since increased GSK-3 activity may be linked to pathol. in diseases such as Alzheimer's disease and non-insulin-dependent diabetes mellitus, several new GSK-3 **inhibitors**, such as the aloisines, the paullones and the maleimides, have been developed. Although they are just starting to be characterized in cell culture expts., these new **inhibitors** hold promise as therapeutic agents.

RE.CNT 160 THERE ARE 160 CITED REFERENCES AVAILABLE FOR THIS RECORD

ALL CITATIONS AVAILABLE IN THE RE FORMAT

AB A review. Glycogen synthase kinase-3 (GSK-3) is a multifunctional serine/threonine kinase found in all eukaryotes. The enzyme is a key regulator of numerous signaling pathways, including cellular responses to Wnt, receptor tyrosine kinases, and G-protein-coupled receptors and is involved in a wide range of cellular processes, ranging from glycogen metab. to cell cycle regulation and proliferation. GSK-3 is unusual in that it is **normally** active in cells and is primarily regulated through **inhibition** of its activity. Another peculiarity compared with other protein kinases is its preference for primed substrates, i.e., substrates previously phosphorylated by another kinase. Several recent advances have improved the understanding of GSK-3 regulation in multiple pathways. These include the soln. of the crystal structure of GSK-3, which has provided insight into GSK-3's penchant for primed substrates and the regulation of GSK-3 by serine phosphorylation, and findings related to the involvement of GSK-3 in the Wnt/.beta.-catenin and **Hedgehog** pathways. Finally, since increased GSK-3 activity may be linked to pathol. in diseases such as Alzheimer's disease and non-insulin-dependent diabetes mellitus, several new GSK-3 **inhibitors**, such as the aloisines, the paullones and the maleimides, have been developed. Although they are just starting to be characterized in cell culture expts., these new **inhibitors** hold promise as therapeutic agents.

L4 ANSWER 8 OF 75 CAPLUS COPYRIGHT 2003 ACS on STN
AN 2003:136895 CAPLUS
DN 138:319057
TI Down-regulation of sonic hedgehog expression in pulmonary hypoplasia is associated with congenital diaphragmatic hernia
AU Unger, Sharon; Copland, Ian; Tibboel, Dick; Post, Martin
CS Lung Biology Research Program, Department of Pediatrics, Hospital for Sick Children Research Institute, University of Toronto, Toronto, Can.
SO American Journal of Pathology (2003), 162(2), 547-555
CODEN: AJPAA4; ISSN: 0002-9440
PB American Society for Investigative Pathology
DT Journal
LA English
AB The pathogenesis of pulmonary hypoplasia assocd. with congenital diaphragmatic hernia (CDH) is unknown. The sonic **hedgehog** (Shh) cascade is crucial for the patterning of the early respiratory system in mice. To establish whether Shh plays a role in the pathogenesis of lung hypoplasia in CDH, we investigated the gestation-specific expression of Shh in **normal** rat and human lungs using in situ hybridization and immunohistochem. The expression pattern was compared with that of age-matched samples of hypoplastic lungs assocd. with CDH in humans and in the 2,4-dichlorophenyl-p-nitrophenylether (nitrofen) rat model. Our results showed that in **normal** controls the expression of Shh increased with advancing gestation, peaked in the late pseudoglandular stage, and declined thereafter. The expression of Shh is initially down-regulated in pulmonary hypoplasia assocd. with CDH and peaks instead during the late canalicular stage. These data indicate that maximal expression of Shh occurs when respiratory bronchioles develop and thinning of the interstitium takes place, suggesting that Shh may play a role in these processes. Furthermore, we obsd. that Shh **inhibited** fetal lung fibroblast proliferation in vitro. Therefore, it is tempting to speculate that alterations in Shh expression may affect these developmental processes, thereby contributing to the pulmonary abnormality in CDH.
RE.CNT 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD

ALL CITATIONS AVAILABLE IN THE RE FORMAT

AB The pathogenesis of pulmonary hypoplasia assocd. with congenital diaphragmatic hernia (CDH) is unknown. The sonic **hedgehog** (Shh) cascade is crucial for the patterning of the early respiratory system in mice. To establish whether Shh plays a role in the pathogenesis of lung hypoplasia in CDH, we investigated the gestation-specific expression of Shh in **normal** rat and human lungs using in situ hybridization and immunohistochem. The expression pattern was compared with that of age-matched samples of hypoplastic lungs assocd. with CDH in humans and in the 2,4-dichlorophenyl-p-nitrophenylether (nitrofen) rat model. Our results showed that in **normal** controls the expression of Shh increased with advancing gestation, peaked in the late pseudoglandular stage, and declined thereafter. The expression of Shh is initially down-regulated in pulmonary hypoplasia assocd. with CDH and peaks instead during the late canalicular stage. These data indicate that maximal expression of Shh occurs when respiratory bronchioles develop and thinning of the interstitium takes place, suggesting that Shh may play a role in these processes. Furthermore, we obsd. that Shh **inhibited** fetal lung fibroblast proliferation in vitro. Therefore, it is tempting to speculate that alterations in Shh expression may affect these developmental processes, thereby contributing to the pulmonary abnormality in CDH.

L4 ANSWER 9 OF 75 CAPLUS COPYRIGHT 2003 ACS on STN
AN 2003:117561 CAPLUS
DN 138:163512
TI Mediators of hedgehog signaling pathways, compositions, and uses related thereto
IN Rubin, Lee; Guicherit, Oivin M.; Price, Stephen; Boyd, Edward A.
PA Curis, Inc., USA
SO PCT Int. Appl., 168 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2003011219	A2	20030213	WO 2002-US24073	20020729

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRAI US 2001-308449P P 20010727
US 2001-338031P P 20011113
OS MARPAT 138:163512
AB The invention provides methods and reagents for **inhibiting** aberrant growth states resulting from **hedgehog** gain-of-function, ptc loss-of-function or smoothened gain-of-function, comprising contacting the cell with a **hedgehog** antagonist, such as a small mol., in a sufficient amt. to aberrant growth state, e.g.,to agonize a **normal** ptc pathway or antagonize smoothened or **hedgehog** activity. Prepn. and testing of a variety of heterocyclic compds. is included. The

effect of benzimidazole deriv. I on a variety of tumor cells (e.g. basal cell carcinoma) was detd.

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L4 ANSWER 10 OF 75 CAPLUS COPYRIGHT 2003 ACS on STN
AN 2002:978471 CAPLUS
DN 138:39182
TI Preparation of substituted benzothiophene derivatives as hedgehog agonists and regulators of cell proliferation and differentiation
IN Baxter, Anthony David; Boyd, Edward Andrew; Guicherit, Oivin M.; Porter, Jeffery; Price, Stephen; Rubin, Lee; Stibbard, John Harry Alexander
PA UK
SO U.S. Pat. Appl. Publ., 130 pp., Cont.-in-part of U.S. Ser. No. 724,492. CODEN: USXXCO
DT Patent
LA English
FAN.CNT 3

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 2002198236	A1	20021226	US 2001-964276	20010926
	US 2003139457	A1	20030724	US 2002-245844	20020917
	WO 2003027234	A2	20030403	WO 2002-US29522	20020918

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRAI	US 2000-193279P	P	20000330
	US 2000-724492	A2	20001128
	WO 2001-US10296	A2	20010330
	US 2001-964276	A2	20010926

OS MARPAT 138:39182

AB Title compds. I [Ar = (hetero)aryl; X = CO, CS, SO2, SO, CH2; Y = absent; Z = absent, aryl, carbocyclyl, heterocyclyl, etc.; M = (un)substituted methylene, etc.; Cy = aryl, heterocyclyl, heteroaryl, cycloalkyl; Cy' = 3-chlorobenzo[b]thiophen-2-yl, 3-fluorobenzo[b]thiophen-2-yl, etc.] are prepd. For instance, N-(4-aminocyclohexyl)-N-methylcarbamic acid tert-Bu ester (prepn. given) was alkylated with 5'-formyl-2'-methoxy-[1,1'-Biphenyl]-4-carbonitrile (MeO3CH, NaBH(OAc)3) and the resulting adduct acylated with 3-chlorobenzo[b]thiophene-2-carbonyl chloride and finally deprotected to give II, which was isolated as the hydrochloride. Methods and reagents are provided for modulating proliferation or differentiation in a cell or tissue, comprising contacting the cell with a **hedgehog** agonist. I are used to correct or **inhibit** an aberrant or unwanted growth state, e.g., by antagonizing a **normal**

ptc pathway or agonizing smoothened or **hedgehog** activity.

AB Title compds. I [Ar = (hetero)aryl; X = CO, CS, SO2, SO, CH2; Y = absent; Z = absent, aryl, carbocyclyl, heterocyclyl, etc.; M = (un)substituted methylene, etc.; Cy = aryl, heterocyclyl, heteroaryl, cycloalkyl; Cy' = 3-chlorobenzo[b]thiophen-2-yl, 3-fluorobenzo[b]thiophen-2-yl, etc.] are prepd. For instance, N-(4-aminocyclohexyl)-N-methylcarbamic acid tert-Bu ester (prepn. given) was alkylated with 5'-formyl-2'-methoxy-[1,1'-Biphenyl]-4-carbonitrile (MeO3CH, NaBH(OAc)3) and the resulting adduct acylated with 3-chlorobenzo[b]thiophene-2-carbonyl chloride and finally deprotected to give II, which was isolated as the hydrochloride. Methods and reagents are provided for modulating proliferation or differentiation in a cell or tissue, comprising contacting the cell with a **hedgehog** agonist. I are used to correct or **inhibit** an aberrant or unwanted growth state, e.g., by antagonizing a **normal** ptc pathway or agonizing smoothened or **hedgehog** activity.

L4 ANSWER 11 OF 75 CAPLUS COPYRIGHT 2003 ACS on STN
AN 2002:963445 CAPLUS
DN 138:215639
TI Differential modulation of BMP signaling promotes the elaboration of cerebral cortical GABAergic neurons or oligodendrocytes from a common sonic hedgehog-responsive ventral forebrain progenitor species
AU Yung, Shau-Yu; Gokhan, Solen; Jurcsak, Jennifer; Molero, Aldrin E.; Abrajano, Joseph J.; Mehler, Mark F.
CS Department of Neuroscience, Rose F. Kennedy Center for Research in Mental Retardation and Developmental Disabilities, Albert Einstein College of Medicine, Bronx, NY, 10461, USA
SO Proceedings of the National Academy of Sciences of the United States of America (2002), 99(25), 16273-16278
CODEN: PNASA6; ISSN: 0027-8424
PB National Academy of Sciences
DT Journal
LA English
AB During cerebral cortical development, excitatory glutamatergic projection neurons are generated from neural stem cells intrinsic to the early embryonic cortical ventricular zone by a process of radial migration, whereas most **inhibitory** .gamma.-aminobutyric acid (GABA)ergic interneurons and oligodendrocytes (OLs) appear to be elaborated from ventral forebrain stem cells that initially undergo tangential cortical migration before terminal lineage maturation. In contrast to the more compartmentalized developmental organization of the spinal cord, the generation of neurons and OLs from a common ventral forebrain stem cell would expose these cells to the sequential actions of ventral and dorsal gradient morphogens [sonic **hedgehog** (Shh) and bone morphogenetic proteins (BMPs)] that **normally** mediate opposing developmental programs. Here we report that Shh promotes GABAergic neuronal/OL lineage restriction of forebrain stem cells, in part, by activation of the basic helix-loop-helix transcription factors, Olig2 and Mash1. In mutant mice with a generalized defect in tangential cortical migration (Dlx1/2-/-), there is a profound and selective redn. in the elaboration of both cortical GABAergic neurons and OLs. Our studies further demonstrate that the sequential elaboration of cortical GABAergic neurons and OLs from common Shh-responsive ventral forebrain progenitors requires the spatial and temporal modulation of cortical BMP signaling by BMP ligands and the BMP antagonist, noggin, resp. These findings suggest an integrative model for cerebral cortical GABAergic neuronal and OL lineage maturation that would incorporate the sequential contributions of the ventral and dorsal forebrain, and the potential role of regional developmental cues in modulating transcriptional codes within evolving neural lineage species.

RE.CNT 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

AB During cerebral cortical development, excitatory glutamatergic projection neurons are generated from neural stem cells intrinsic to the early embryonic cortical ventricular zone by a process of radial migration, whereas most **inhibitory** .gamma.-aminobutyric acid (GABA)ergic interneurons and oligodendrocytes (OLs) appear to be elaborated from ventral forebrain stem cells that initially undergo tangential cortical migration before terminal lineage maturation. In contrast to the more compartmentalized developmental organization of the spinal cord, the generation of neurons and OLs from a common ventral forebrain stem cell would expose these cells to the sequential actions of ventral and dorsal gradient morphogens [sonic **hedgehog** (Shh) and bone morphogenetic proteins (BMPs)] that **normally** mediate opposing developmental programs. Here we report that Shh promotes GABAergic neuronal/OL lineage restriction of forebrain stem cells, in part, by activation of the basic helix-loop-helix transcription factors, Olig2 and Mash1. In mutant mice with a generalized defect in tangential cortical migration (Dlx1/2-/-), there is a profound and selective redn. in the elaboration of both cortical GABAergic neurons and OLs. Our studies further demonstrate that the sequential elaboration of cortical GABAergic neurons and OLs from common Shh-responsive ventral forebrain progenitors requires the spatial and temporal modulation of cortical BMP signaling by BMP ligands and the BMP antagonist, noggin, resp. These findings suggest an integrative model for cerebral cortical GABAergic neuronal and OL lineage maturation that would incorporate the sequential contributions of the ventral and dorsal forebrain, and the potential role of regional developmental cues in modulating transcriptional codes within evolving neural lineage species.

L4 ANSWER 12 OF 75 CAPLUS COPYRIGHT 2003 ACS on STN
AN 2002:955072 CAPLUS
DN 138:184287
TI Bone morphogenetic proteins negatively control oligodendrocyte precursor specification in the chick spinal cord
AU Mekki-Dauriac, Soraya; Agius, Eric; Kan, Paulette; Cochard, Philippe
CS Centre de Biologie du Developpement, UMR 5547 CNRS/UPS, Universite Paul Sabatier, Toulouse, 31062, Fr.
SO Development (Cambridge, United Kingdom) (2002), 129(22), 5117-5130
CODEN: DEVPED; ISSN: 0950-1991
PB Company of Biologists Ltd.
DT Journal
LA English
AB In the vertebrate spinal cord, oligodendrocytes originate from a restricted region of the ventral neuroepithelium. This ventral localization of oligodendrocyte precursors (OLPs) depends on the inductive influence of sonic **hedgehog** (Shh) secreted by ventral midline cells. The authors have investigated whether the ventral restriction of OLP specification might also depend on **inhibiting** signals mediated by bone morphogenetic proteins (BMPs). BMPs invariably and markedly **inhibited** oligodendrocyte development in ventral neural tissue both in vitro and in vivo. Conversely, in vivo ablation of the dorsal most part of the chick spinal cord or inactivation of BMP signaling using grafts of noggin-producing cells promoted the appearance of neuroepithelial OLPs dorsal to their **normal** domain of emergence, showing that endogenous BMPs contribute to the **inhibition** of oligodendrocyte development in the spinal cord. BMPs were able to oppose the Shh-mediated induction of OLPs in spinal cord neuroepithelial explants dissected before oligodendrocyte induction, suggesting that BMPs may repress OLP specification by interfering with Shh signaling in vivo.

Strikingly, among the transcription factors involved in OLP specification, BMP treatment strongly **inhibited** the expression of Olig2 but not of Nkx2.2, suggesting that BMP-mediated **inhibition** of oligodendrogenesis is controlled through the repression of the former transcription factor. Altogether, the authors' data show that oligodendrogenesis is not only regulated by ventral inductive signals such as Shh, but also by dorsal **inhibiting** signals including BMP factors. They suggest that the dorsoventral position of OLPs depends on a tightly regulated balance between Shh and BMP activities.

RE.CNT 71 THERE ARE 71 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

AB In the vertebrate spinal cord, oligodendrocytes originate from a restricted region of the ventral neuroepithelium. This ventral localization of oligodendrocyte precursors (OLPs) depends on the inductive influence of sonic **hedgehog** (Shh) secreted by ventral midline cells. The authors have investigated whether the ventral restriction of OLP specification might also depend on **inhibiting** signals mediated by bone morphogenetic proteins (BMPs). BMPs invariably and markedly **inhibited** oligodendrocyte development in ventral neural tissue both in vitro and in vivo. Conversely, in vivo ablation of the dorsal most part of the chick spinal cord or inactivation of BMP signaling using grafts of noggin-producing cells promoted the appearance of neuroepithelial OLPs dorsal to their **normal** domain of emergence, showing that endogenous BMPs contribute to the **inhibition** of oligodendrocyte development in the spinal cord. BMPs were able to oppose the Shh-mediated induction of OLPs in spinal cord neuroepithelial explants dissected before oligodendrocyte induction, suggesting that BMPs may repress OLP specification by interfering with Shh signaling in vivo. Strikingly, among the transcription factors involved in OLP specification, BMP treatment strongly **inhibited** the expression of Olig2 but not of Nkx2.2, suggesting that BMP-mediated **inhibition** of oligodendrogenesis is controlled through the repression of the former transcription factor. Altogether, the authors' data show that oligodendrogenesis is not only regulated by ventral inductive signals such as Shh, but also by dorsal **inhibiting** signals including BMP factors. They suggest that the dorsoventral position of OLPs depends on a tightly regulated balance between Shh and BMP activities.

L4 ANSWER 13 OF 75 CAPLUS COPYRIGHT 2003 ACS on STN
AN 2002:860103 CAPLUS
DN 138:299400
TI The transcription factor Sox9 has essential roles in successive steps of the chondrocyte differentiation pathway and is required for expression of Sox5 and Sox6
AU Akiyama, Haruhiko; Chaboissier, Marie-Christine; Martin, James F.; Schedl, Andreas; de Crombrugghe, Benoit
CS Department of Molecular Genetics, The University of Texas M.D. Anderson Cancer Center, Houston, TX, 77030, USA
SO Genes & Development (2002), 16(21), 2813-2828
CODEN: GEDEEP; ISSN: 0890-9369
PB Cold Spring Harbor Laboratory Press
DT Journal
LA English
AB To examine whether the transcription factor Sox9 has an essential role during the sequential steps of chondrocyte differentiation, we have used the Cre/loxP recombination system to generate mouse embryos in which either Sox9 is missing from undifferentiated mesenchymal cells of limb buds or the Sox9 gene is inactivated after chondrogenic mesenchymal condensations. Inactivation of Sox9 in limb buds before mesenchymal

condensations resulted in a complete absence of both cartilage and bone, but markers for the different axes of limb development showed a **normal** pattern of expression. Apoptotic domains within the developing limbs were expanded, suggesting that Sox9 suppresses apoptosis. Expression of Sox5 and Sox6, two other Sox genes involved in chondrogenesis, was no longer detected. Moreover, expression of Runx2, a transcription factor needed for osteoblast differentiation, was also abolished. Embryos, in which Sox9 was deleted after mesenchymal condensations, exhibited a severe generalized chondrodysplasia, similar to that in Sox5; Sox6 double-null mutant mice. Most cells were arrested as condensed mesenchymal cells and did not undergo overt differentiation into chondrocytes. Furthermore, chondrocyte proliferation was severely **inhibited** and joint formation was defective. Although Indian **hedgehog**, Patched1, parathyroid hormone-related peptide (Pthrp), and Pth/Pthrp receptor were expressed, their expression was down-regulated. Our expts. further suggested that Sox9 is also needed to prevent conversion of proliferating chondrocytes into hypertrophic chondrocytes. We conclude that Sox9 is required during sequential steps of the chondrocyte differentiation pathway.

RE.CNT 47 THERE ARE 47 CITED REFERENCES AVAILABLE FOR THIS RECORD
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L4 ANSWER 14 OF 75 CAPLUS COPYRIGHT 2003 ACS on STN
AN 2002:655918 CAPLUS
DN 138:20324
TI Alternative first exons of PTCH1 are differentially regulated in vivo and may confer different functions to the PTCH1 protein
AU Kogerman, Priit; Krause, Darren; Rahnama, Fahimeh; Kogerman, Lembi; Unden, Anne Birgitte; Zaphiropoulos, Peter G.; Toftgard, Rune
CS Department of Biosciences at Novum, Karolinska Institutet, Huddinge, Swed.
SO Oncogene (2002), 21(39), 6007-6016
CODEN: ONCNES; ISSN: 0950-9232
PB Nature Publishing Group
DT Journal

LA English
AB The PTCH1 gene is a human tumor suppressor gene frequently mutated in basal cell carcinoma (BCC) and several other tumor types. It encodes a receptor for sol. factors of the **hedgehog** family. Binding of **hedgehog** to the receptor relieves its **inhibitory** action on the transmembrane co-receptor Smoh. In this study we describe alternative first exons of the PTCH1 tumor suppressor gene and show that they are differentially regulated in **normal** tissues, exon 1B being expressed at very low levels and the major mRNA species contg. exon 1 or 1A. Exon 1B transcripts were found to be specifically upregulated in nodular BCCs. The different PTCH1 transcripts all encode proteins that interact with Smoh in doubly transfected cells. Furthermore, functional assays demonstrated that whereas all PTCH1 isoforms can **inhibit** the activity of SHH, only the PTCH1B isoform is capable of fully **inhibiting** Smoh activity. The results indicate that in tumor cells the PTCH1B promoter is specifically activated and importantly, that the N-terminal part of PTCH1 including exon 1B is required for full **inhibition** of Smoh signaling but not for phys. interaction with Smoh.
RE.CNT 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT
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L4 ANSWER 15 OF 75 CAPLUS COPYRIGHT 2003 ACS on STN
AN 2002:631673 CAPLUS
DN 137:349856
TI Patched acts catalytically to suppress the activity of Smoothened
AU Taipale, J.; Cooper, M. K.; Maiti, T.; Beachy, P. A.
CS Department of Molecular Biology and Genetics, Howard Hughes Medical Institute, Johns Hopkins University School of Medicine, Baltimore, MD, 21205, USA
SO Nature (London, United Kingdom) (2002), 418(6900), 892-896
CODEN: NATUAS; ISSN: 0028-0836
PB Nature Publishing Group
DT Journal
LA English
AB Mutations affecting the transmembrane proteins Patched (Ptc) or Smoothened (Smo) that trigger ligand-independent activity of the **Hedgehog** (Hh) signaling pathway are assocd. with human tumors such as basal cell carcinoma (BCC) and medulloblastoma. Despite extensive genetic studies demonstrating the importance of these receptor components in embryonic patterning and cancer, the mechanism by which Ptc regulates Smo is not

understood. Here we report that Ptc and Smo are not significantly assocd. within Hh-responsive cells. Furthermore, we show that free Ptc (unbound by Hh) acts sub-stoichiometrically to suppress Smo activity and thus is crit. in specifying the level of pathway activity. Patched is a twelve-transmembrane protein with homol. to bacterial proton-driven transmembrane mol. transporters; we demonstrate that the function of Ptc is impaired by alterations of residues that are conserved in and required for function of these bacterial transporters. These results suggest that the Ptc tumor suppressor functions **normally** as a transmembrane mol. transporter, which acts indirectly to **inhibit** Smo activity, possibly through changes in distribution or concn. of a small mol.

RE.CNT 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD
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L4 ANSWER 16 OF 75 CAPLUS COPYRIGHT 2003 ACS on STN
AN 2002:613019 CAPLUS
DN 137:184414
TI Sonic hedgehog promotes cell cycle progression in activated peripheral CD4+ T lymphocytes
AU Lowrey, Jacqueline A.; Stewart, Gareth A.; Lindey, Susannah; Hoyne, Gerard F.; Dallman, Margaret J.; Howie, Sarah E. M.; Lamb, Jonathan R.
CS Immunobiology Group, Medical Research Council Center for Inflammation Research, Respiratory Medicine Unit, University of Edinburgh Medical School, Edinburgh, EH8 9AG, UK
SO Journal of Immunology (2002), 169(4), 1869-1875
CODEN: JOIMA3; ISSN: 0022-1767
PB American Association of Immunologists
DT Journal
LA English
AB Sonic **hedgehog** (Shh) signaling is important in the growth and differentiation of many cell types and recently has been reported to play a role in T cell development in the thymus. This prompted us to investigate whether or not Shh contributes to the clonal expansion of peripheral CD4+ T cells. In this study, we demonstrate that Shh and other components of the signaling pathway patched, smoothened, and Gli1 (glioma-assocd. oncogene) are expressed in peripheral CD4+ T cells. The addn. of the biol. active amino-terminal Shh peptide had no effect on resting CD4+ T cells, but significantly enhanced proliferation of anti-CD3/28 Ab-activated CD4+ T cells. This was not due to antiapoptotic effects, but by promoting entry of T cells into the S-G2 proliferative phase of the cell cycle. Neutralizing anti-Shh Ab reduced T cell proliferation by **inhibiting** cell transition into the S-G2 phase,

suggesting that endogenously produced Shh plays a physiol. role in the clonal expansion of T cells. Furthermore, we have obsd. a significant up-regulation of Shh and Gli1 (glioma-assocd. oncogene) mRNA in activated CD4+ T cells with or without addn. of exogenous Shh, which corresponds with maximal CD4+ T cell proliferation, whereas bcl-2 was only upregulated in activated cells in the presence of Shh. Our findings suggest that endogenously produced Shh may play a role in sustaining **normal** CD4+ T cell proliferation and exogenously added Shh enhances this response.

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L4 ANSWER 17 OF 75 CAPLUS COPYRIGHT 2003 ACS on STN
AN 2002:612915 CAPLUS
DN 138:202199
TI In vivo enhanced expression of patched dampens the sonic hedgehog pathway
AU Bergstein, Ivan; Leopold, Philip L.; Sato, Noboru; Panteleyev, Andrei A.; Christiano, Angela M.; Crystal, Ronald G.
CS Division of Pulmonary and Critical Care Medicine, Division of Hematology-Oncology, Weill Medical College of Cornell University, New York, NY, 10021, USA
SO Molecular Therapy (2002), 6(2), 258-264
CODEN: MTOHCK; ISSN: 1525-0016
PB Elsevier Science
DT Journal
LA English
AB The sonic **hedgehog** (SHH)-patched (PTCH) pathway functions in **normal** embryonic development of the brain, musculoskeletal system, and hair follicles, and in **normal** post-natal control of hair follicles. Dysregulation of the pathway has been implicated in a variety of neoplasias, including those of skin and brain. Based on the knowledge that generalized, prolonged PTCH expression can **inhibit** the effects of SHH signaling, we tested the hypothesis that localized transient overexpression of PTCH would **inhibit** the phenotype of SHH-induced accelerated growth of hair follicles. Adenovirus (Ad)-mediated transient over-expression of Shh (AdShh) in telogen (8 wk) mouse skin induced anagen hair growth as demonstrated by histol. and gross

appearance. Strikingly, local intradermal administration of a Ptch-expressing adenovirus (AdPtch), but not a Null control adenovirus (AdNull), 18 h before AdShh injection, significantly blocked this phenotype, with 100% of AdPtch + AdShh mice failing to advance to anagen compared with AdNull + AdShh mice and AdShh mice (30% and 45% failing to advance to anagen, resp.). Thus, PTCH expression mediated by gene transfer can modulate the SHH signaling pathway in the adult mammal and may serve as a starting point for therapies relevant to clin. conditions resulting from dysregulation of this pathway as well as for strategies to suppress **normal** SHH-dependent processes, such as hair growth.

RE.CNT 60 THERE ARE 60 CITED REFERENCES AVAILABLE FOR THIS RECORD
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L4 ANSWER 18 OF 75 CAPLUS COPYRIGHT 2003 ACS on STN
AN 2002:601056 CAPLUS
DN 137:335838
TI CUSP/p63 expression in basal cell carcinoma
AU Dellavalle, R. P.; Walsh, P.; Marchbank, A.; Grayson, T. E.; Su, L.-J.; Parker, E. R.; DeGregori, J.; Penheiter, K.; Aszterbaum, M.; Epstein, E. H., Jr.; Lee, L. A.
CS Department of Dermatology, University of Colorado School of Medicine, Denver, CO, USA
SO Experimental Dermatology (2002), 11(3), 203-208
CODEN: EXDEEY; ISSN: 0906-6705
PB Blackwell Munksgaard
DT Journal
LA English
AB Chronic ulcerative stomatitis protein (CUSP), the most abundant cutaneous isoform of p63, is a p53-related gene essential for epithelial development. CUSP lacks the N-terminal transactivation domain found on other p53 family members and has been shown to **inhibit** p53 function in vitro. In this study, biopsies of **normal** skin (21 of 21), benign neoplasms [seborrheic keratosis (3 of 3), acrochordon (2 of 3), and verruca plana (3 of 3)], and squamous cell carcinomas (SCC) (4 of 4) displayed strong nuclear CUSP immuno-reactivity in epidermal cells. In contrast few basal cell carcinomas (BCC) (7 of 27) and sebaceous nevi (1 of 2) displayed this pattern of CUSP immunoreactivity. Thus, biopsies of cutaneous conditions characterized by sonic **hedgehog** (SHH)

pathway dysregulation were more than 86 times as likely to lack CUSP/p63 immunofluorescence as were other cutaneous samples. Adjacent **normal**-appearing skin from patients with basal cell nevus syndrome (BCNS) (2 of 3) also lacked CUSP immuno-staining. Lastly, a BCC arising in a patched heterozygous mouse also lacked CUSP immuno-staining. Because CUSP mRNA and protein were detected via Northern and Western anal. in BCC samples lacking CUSP immuno-staining, we sequenced the coding region of CUSP from two non-staining BCCs but found no mutations. Therefore, CUSP appears to be present, unmutated, and yet frequently undetectable by immunofluorescence in cutaneous lesions in both humans and mice that are assocd. with SHH pathway dysregulation (BCCs, BCNS, and nevus sebaceous).

RE.CNT 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD
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L4 ANSWER 19 OF 75 CAPLUS COPYRIGHT 2003 ACS on STN
AN 2002:432006 CAPLUS
DN 137:260515
TI Disruption of Testis Cords by Cyclopamine or Forskolin Reveals Independent Cellular Pathways in Testis Organogenesis
AU Yao, Humphrey Hung-Chang; Capel, Blanche
CS Department of Cell Biology, Duke University Medical Center, Durham, NC, 27710, USA
SO Developmental Biology (Orlando, FL, United States) (2002), 246(2), 356-365
CODEN: DEBIAO; ISSN: 0012-1606
PB Elsevier Science
DT Journal
LA English
AB Most studies to date indicate that the formation of testis cords is crit. for proper Sertoli cell differentiation, **inhibition** of germ cell meiosis, and regulation of Leydig cell differentiation. However, the connections between these events are poorly understood. The objective of this study was to dissect the mol. and cellular relationships between these events in testis formation. We took advantage of the different effects of two **hedgehog** signaling **inhibitors**, cyclopamine and forskolin, on gonad explant cultures. Both **hedgehog inhibitors** phenocopied the disruptive effect of Dhh-/- on formation of testis cords without influencing Sertoli cell

differentiation. However, they exhibited different effects on other cellular events during testis development. Treatment with cyclopamine did not affect **inhibition** of germ cell meiosis and mesonephric cell migration but caused defects in Leydig cell differentiation. In contrast, forskolin treatment induced germ cell meiosis, **inhibited** mesonephric cell migration, and had no effect on Leydig cell differentiation. By carefully contrasting the different effects of these two **hedgehog inhibitors**, we demonstrate that, although formation of testis cords and development of other cell types **normally** take place in a tightly regulated sequence, each of these events can occur independent of the others.

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AB Most studies to date indicate that the formation of testis cords is crit. for proper Sertoli cell differentiation, **inhibition** of germ cell meiosis, and regulation of Leydig cell differentiation. However, the connections between these events are poorly understood. The objective of this study was to dissect the mol. and cellular relationships between these events in testis formation. We took advantage of the different effects of two **hedgehog** signaling **inhibitors**, cyclopamine and forskolin, on gonad explant cultures. Both **hedgehog inhibitors** phenocopied the disruptive effect of Dhh-/- on formation of testis cords without influencing Sertoli cell differentiation. However, they exhibited different effects on other cellular events during testis development. Treatment with cyclopamine did not affect **inhibition** of germ cell meiosis and mesonephric cell migration but caused defects in Leydig cell differentiation. In contrast, forskolin treatment induced germ cell meiosis, **inhibited** mesonephric cell migration, and had no effect on Leydig cell differentiation. By carefully contrasting the different effects of these two **hedgehog inhibitors**, we demonstrate that, although formation of testis cords and development of other cell types **normally** take place in a tightly regulated sequence, each of these events can occur independent of the others.

L4 ANSWER 20 OF 75 CAPLUS COPYRIGHT 2003 ACS on STN
AN 2002:394641 CAPLUS
DN 137:182834
TI Heparan sulfate proteoglycans and spinal neurulation in the mouse embryo
AU Yip, George W.; Ferretti, Patrizia; Copp, Andrew J.
CS Developmental Biology Unit, Institute of Child Health, University College London, London, UK
SO Development (Cambridge, United Kingdom) (2002), 129(9), 2109-2119
CODEN: DEVPED; ISSN: 0950-1991
PB Company of Biologists Ltd.
DT Journal
LA English
AB Heparan sulfate proteoglycans have been implicated in the binding and presentation of several growth factors to their receptors, thereby regulating cellular growth and differentiation. To investigate the role of heparan sulfate proteoglycans in mouse spinal neurulation, we administered chlorate, a competitive **inhibitor** of glycosaminoglycan sulfation, to cultured E8.5 embryos. Treated embryos exhibit accelerated posterior neuropore closure, accompanied by suppression of neuroepithelial bending at the median hinge point and accentuated bending at the paired dorsolateral hinge points of the posterior neuropore. These effects appear specific, as they can be prevented by addn. of heparan sulfate to the culture medium, whereas heparitinase-treated heparan sulfate and chondroitin sulfate are

ineffective. Both N- and O-sulfate groups appear to be necessary for the action of heparan sulfate. In situ hybridization anal. demonstrates a **normal** distribution of sonic **hedgehog** mRNA in chlorate-treated embryos. By contrast, patched 1 transcripts are abnormally abundant in the notochord, and diminished in the overlying neuroepithelium, suggesting that sonic **hedgehog** signalling from the notochord may be perturbed by **inhibition** of heparan sulfation. Together, these results demonstrate a regulatory role for heparan sulfate in mouse spinal neurulation.

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L4 ANSWER 21 OF 75 CAPLUS COPYRIGHT 2003 ACS on STN
AN 2002:352492 CAPLUS
DN 137:91140
TI c-Myc overexpression increases cell size and impairs cartilage differentiation during chick limb development
AU Piedra, M. Elisa; Delgado, M. Dolores; Ros, Maria A.; Leon, Javier
CS Departamento de Anatomia y Biologia Celular, Universidad de Cantabria, Santander, 39011, Spain
SO Cell Growth & Differentiation (2002), 13(4), 185-193
CODEN: CGDIE7; ISSN: 1044-9523
PB American Association for Cancer Research
DT Journal
LA English

AB C-Myc is a transcription factor involved in the control of cell proliferation, differentiation, and apoptosis, all basic processes for embryogenesis. To analyze c-Myc roles in limb development, the authors overexpressed c-myc in chick embryos using a retroviral vector. Forced c-myc expression resulted in enlarged limbs, because of an increase in cell size not accompanied by modifications in cell proliferation. However, at later stages, limbs overexpressing c-myc showed a marked shortening of their skeletal elements, because of the **inhibition** of chondrocyte maturation. C-Myc interfered with chondrogenesis, independently of the Indian **hedgehog**/parathyroid hormone-related protein and Wnt5a/Wnt5b regulatory loops. C-myc-infected limbs also exhibited patterning defects, such as extraphalangeal elements and delayed interdigital apoptosis that occasionally led to interdigital

chondrogenesis. In contrast, c-myc overexpression did not interfere with other processes, such as muscle differentiation. Although based on overexpression expts., the authors' results suggest that endogenous c-Myc may be implicated in the control of cell size and skeletal differentiation during **normal** limb development.

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L4 ANSWER 22 OF 75 CAPLUS COPYRIGHT 2003 ACS on STN
AN 2002:293442 CAPLUS
DN 136:325823
TI Preparation and formulation of proline derivatives as mediators of hedgehog signaling pathways for pharmaceutical and cosmetic uses
IN Baxter, Anthony D.; Boyd, Edward A.; Guicherit, Oivin M.; Price, Stephen; Rubin, Lee D.
PA Curis, Inc., USA
SO PCT Int. Appl., 230 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 4

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002030421	A2	20020418	WO 2001-US32054	20011012
	WO 2002030421	A3	20020926		
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	US 6552016	B1	20030422	US 2000-688018	20001013
	AU 2002011713	A5	20020422	AU 2002-11713	20011012
	US 2002165221	A1	20021107	US 2001-977096	20011012
	EP 1326600	A2	20030716	EP 2001-979788	20011012
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
PRAI	US 2000-240536P	P	20001013		

US 1999-159417P P 19991014
US 2000-196543P P 20000411
US 2000-211919P P 20000616
US 2000-240564P P 20001013
WO 2001-US32054 W 20011012
OS MARPAT 136:325823
AB Proline-based compds. such as I [R1, R4 = H, alkyl, (CH2)n-(hetero)aryl (n = 0-5); L = null, -(CH2)n-, -alkenyl-, -alkynyl-, -(CH2)n-alkenyl-, -(CH2)n-alkynyl-, -(CH2)nO(CH2)p-, -(CH2)nNR8(CH2)p-, -(CH2)nS(CH2)p-, -(CH2)nalkenyl(CH2)p-, -(CH2)nalkynyl(CH2)p-, -O(CH2)n-,-NR8(CH2)n-, or -S(CH2)n- (R8 is any group given for R1 or two R8 together may form a 4- to 8-membered ring; p = 0-3); X, D = NR8, O, S, NR8NR8, ONR8, or a direct bond; Y, Z = O or S; E represents NR5, where R5 represents LR8 or an ammonium salt; X1, X2 = null, CH2 or CH2CH2] were prepd. for pharmaceutical and cosmetic use. Thus, proline deriv. II was prepd. via a multistep synthetic sequence which started with trans-4-hydroxy-L-proline, 3-methoxybenzaldehyde, piperonal, tert-butylacetyl chloride, and N-(tert-butoxycarbonyl)piperazine. The prepd. proline derivs. were tested for agonist activity for **inhibiting** aberrant growth states resulting from **hedgehog** gain-of-function, ptc loss-of-function or smoothened gain-of-function comprising contacting the cell with a **hedgehog** antagonist, such as a small mol., in a sufficient amt. to aberrant growth state, e.g., to agonize a **normal** ptc pathway or antagonize smoothened or **hedgehog** activity.
AB Proline-based compds. such as I [R1, R4 = H, alkyl, (CH2)n-(hetero)aryl (n = 0-5); L = null, -(CH2)n-, -alkenyl-, -alkynyl-, -(CH2)n-alkenyl-, -(CH2)n-alkynyl-, -(CH2)nO(CH2)p-, -(CH2)nNR8(CH2)p-, -(CH2)nS(CH2)p-, -(CH2)nalkenyl(CH2)p-, -(CH2)nalkynyl(CH2)p-, -O(CH2)n-,-NR8(CH2)n-, or -S(CH2)n- (R8 is any group given for R1 or two R8 together may form a 4- to 8-membered ring; p = 0-3); X, D = NR8, O, S, NR8NR8, ONR8, or a direct bond; Y, Z = O or S; E represents NR5, where R5 represents LR8 or an ammonium salt; X1, X2 = null, CH2 or CH2CH2] were prepd. for pharmaceutical and cosmetic use. Thus, proline deriv. II was prepd. via a multistep synthetic sequence which started with trans-4-hydroxy-L-proline, 3-methoxybenzaldehyde, piperonal, tert-butylacetyl chloride, and N-(tert-butoxycarbonyl)piperazine. The prepd. proline derivs. were tested for agonist activity for **inhibiting** aberrant growth states resulting from **hedgehog** gain-of-function, ptc loss-of-function or smoothened gain-of-function comprising contacting the cell with a **hedgehog** antagonist, such as a small mol., in a sufficient amt. to aberrant growth state, e.g., to agonize a **normal** ptc pathway or antagonize smoothened or **hedgehog** activity.

L4 ANSWER 23 OF 75 CAPLUS COPYRIGHT 2003 ACS on STN
AN 2002:172887 CAPLUS
DN 137:107138
TI Expression of a sonic hedgehog signal transducer, hedgehog-interacting protein, by human basal cell carcinoma
AU Tojo, M.; Kiyosawa, H.; Iwatsuki, K.; Kaneko, F.
CS Departments of Dermatology, Fukushima Medical University School of Medicine, Fukushima, 960-1295, Japan
SO British Journal of Dermatology (2002), 146(1), 69-73
CODEN: BJDEAZ; ISSN: 0007-0963
PB Blackwell Science Ltd.
DT Journal
LA English
AB Aberrant activation of the **hedgehog** pathway was identified in various human tumors, including familial and sporadic basal cell carcinomas (BCCs). It was postulated that binding of sonic

hedgehog protein (SHH) to its receptor, patched protein (PTC), releases the **inhibitory** effect of PTC against smoothened protein (SMO), another protein of the SHH signaling pathway. The pos. SMO signaling is not downregulated in BCCs because of the mutational inactivation of PTC. Recently, **hedgehog**-interacting protein (HIP) was found to bind to SHH directly and attenuate SHH signaling like PTC, while its expression was induced by SHH signals. To examine the expression patterns of HIP, SHH and PTC gene mRNA by human BCCs, in comparison with those by **normal** human skin and various skin tumors. We performed quant. reverse transcriptase-polymerase chain reaction analyses with a series of samples from BCCs, other skin tumors and **normal** skin. We found that the mRNA expression of both HIP and PTC genes was enhanced in all samples of BCCs, whereas none of the other skin tumors tested exhibited an increased level of such mRNAs as compared with **normal** skin. The transcription of the SHH gene, however, was at a baseline level in most BCCs. These results indicate that both HIP and PTC gene expression are specifically involved in the development of BCCs, and that the prodn. of HIP is linked with the expression of the PTC gene but not the SHH gene.

RE.CNT 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

AB Aberrant activation of the **hedgehog** pathway was identified in various human tumors, including familial and sporadic basal cell carcinomas (BCCs). It was postulated that binding of sonic **hedgehog** protein (SHH) to its receptor, patched protein (PTC), releases the **inhibitory** effect of PTC against smoothened protein (SMO), another protein of the SHH signaling pathway. The pos. SMO signaling is not downregulated in BCCs because of the mutational inactivation of PTC. Recently, **hedgehog**-interacting protein (HIP) was found to bind to SHH directly and attenuate SHH signaling like PTC, while its expression was induced by SHH signals. To examine the expression patterns of HIP, SHH and PTC gene mRNA by human BCCs, in comparison with those by **normal** human skin and various skin tumors. We performed quant. reverse transcriptase-polymerase chain reaction analyses with a series of samples from BCCs, other skin tumors and **normal** skin. We found that the mRNA expression of both HIP and PTC genes was enhanced in all samples of BCCs, whereas none of the other skin tumors tested exhibited an increased level of such mRNAs as compared with **normal** skin. The transcription of the SHH gene, however, was at a baseline level in most BCCs. These results indicate that both HIP and PTC gene expression are specifically involved in the development of BCCs, and that the prodn. of HIP is linked with the expression of the PTC gene but not the SHH gene.

L4 ANSWER 24 OF 75 CAPLUS COPYRIGHT 2003 ACS on STN
AN 2002:78114 CAPLUS
DN 136:260893
TI The Sonic Hedgehog-Gli pathway regulates dorsal brain growth and tumorigenesis
AU Dahmane, Nadia; Sanchez, Pilar; Gitton, Yorick; Palma, Veronica; Sun, Tao; Beyna, Mercedes; Weiner, Howard; Ruiz i Altaba, Ariel
CS Skirball Institute of Biomolecular Medicine, Developmental Genetics Program and Department of Cell Biology, NYU School of Medicine, New York, NY, 10016, USA
SO Development (Cambridge, United Kingdom) (2001), 128(24), 5201-5212
CODEN: DEVPED; ISSN: 0950-1991
PB Company of Biologists Ltd.
DT Journal
LA English

AB The mechanisms that regulate the growth of the brain remain unclear. We show that Sonic **hedgehog** (Shh) is expressed in a layer-specific manner in the perinatal mouse neocortex and tectum, whereas the Gli genes, which are targets and mediators of SHH signaling, are expressed in proliferative zones. In vitro and in vivo assays show that SHH is a mitogen for neocortical and tectal precursors and that it modulates cell proliferation in the dorsal brain. Together with its role in the cerebellum, our findings indicate that SHH signaling unexpectedly controls the development of the three major dorsal brain structures. We also show that a variety of primary human brain tumors and tumor lines consistently express the GLI genes and that cyclopamine, a SHH signaling **inhibitor**, **inhibits** the proliferation of tumor cells. Using the in vivo tadpole assay system, we further show that misexpression of GLI1 induces CNS hyperproliferation that depends on the activation of endogenous Gli1 function. SHH-GLI signaling thus modulates **normal** dorsal brain growth by controlling precursor proliferation, an evolutionarily important and plastic process that is deregulated in brain tumors.

RE.CNT 73 THERE ARE 73 CITED REFERENCES AVAILABLE FOR THIS RECORD
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L4 ANSWER 25 OF 75 CAPLUS COPYRIGHT 2003 ACS on STN
AN 2002:18913 CAPLUS
DN 136:181098
TI Suppression of hair follicle development inhibits induction of sonic hedgehog, patched, and patched-2 in hair germs in mice
AU Yamago, Gabriela; Takata, Yoshimi; Furuta, Isao; Urase, Koko; Momoi, Takashi; Huh, Nam-ho
CS Department of Cell Biology, Okayama University Graduate School of Medicine and Dentistry, Okayama, 700-8558, Japan
SO Archives of Dermatological Research (2001), 293(9), 435-441
CODEN: ADREDL; ISSN: 0340-3696
PB Springer-Verlag
DT Journal
LA English
AB Embryonic induction of hair follicles is a fascinating model of localized morphogenesis from a simple homogeneous epithelial cell sheet. Accumulating evidence indicates that Sonic **hedgehog** (Shh) signaling plays a central role in hair follicle formation. The authors quantitated the expression levels of Shh and its receptor genes, Patched (Ptc) and Patched-2 (Ptch2), in two distinct exptl. systems in which the

development of hair follicles was suppressed. Shh, Ptc, and Ptch2 were induced about six- to tenfold in **normal** embryonic hair germs in vivo as well as in developing skin tissue maintained in organ culture. This induction was almost completely **inhibited** both in the developing skin tissue of ICR mice cultured with 30 ng/mL epidermal growth factor and in embryos of Tabby mutant mice (a model of hypohidrotic ectodermal dysplasia) at 14.5-15.5 days postcoitus. Expression of Shh, Ptc and Ptch2 was induced in the Tabby embryos at 16.5 days postcoitus, indicating that Shh signaling may be involved in the formation not only of the well-studied guard hair but also of the awl hair. The potential of the two biol. systems for studying mol. mechanisms in hair follicle formation, particularly at an early phase including Shh signaling, is discussed.

RE.CNT 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

AB Embryonic induction of hair follicles is a fascinating model of localized morphogenesis from a simple homogeneous epithelial cell sheet. Accumulating evidence indicates that Sonic **hedgehog** (Shh) signaling plays a central role in hair follicle formation. The authors quantitated the expression levels of Shh and its receptor genes, Patched (Ptc) and Patched-2 (Ptch2), in two distinct exptl. systems in which the development of hair follicles was suppressed. Shh, Ptc, and Ptch2 were induced about six- to tenfold in **normal** embryonic hair germs in vivo as well as in developing skin tissue maintained in organ culture. This induction was almost completely **inhibited** both in the developing skin tissue of ICR mice cultured with 30 ng/mL epidermal growth factor and in embryos of Tabby mutant mice (a model of hypohidrotic ectodermal dysplasia) at 14.5-15.5 days postcoitus. Expression of Shh, Ptc and Ptch2 was induced in the Tabby embryos at 16.5 days postcoitus, indicating that Shh signaling may be involved in the formation not only of the well-studied guard hair but also of the awl hair. The potential of the two biol. systems for studying mol. mechanisms in hair follicle formation, particularly at an early phase including Shh signaling, is discussed.

L4 ANSWER 26 OF 75 CAPLUS COPYRIGHT 2003 ACS on STN
AN 2001:905689 CAPLUS
DN 136:99869
TI BMP and Ihh/PTHrP signaling interact to coordinate chondrocyte proliferation and differentiation
AU Minina, Eleonora; Wenzel, Hans Markus; Kreschel, Conny; Karp, Seth; Gaffield, William; McMahon, Andrew P.; Vortkamp, Andrea
CS Otto Warburg-Laboratory, Max-Planck-Institute for Molecular Genetics, Berlin, 14195, Germany
SO Development (Cambridge, United Kingdom) (2001), 128(22), 4523-4534
CODEN: DEVPED; ISSN: 0950-1991
PB Company of Biologists Ltd.
DT Journal
LA English
AB During endochondral ossification, two secreted signals, Indian **hedgehog** (Ihh) and parathyroid hormone-related protein (PTHrP), have been shown to form a neg. feedback loop regulating the onset of hypertrophic differentiation of chondrocytes. Bone morphogenetic proteins (BMPs), another family of secreted factors regulating bone formation, have been implicated as potential interactors of the Ihh/PTHrP feedback loop. To analyze the relationship between the two signaling pathways, we used an organ culture system for limb explants of mouse and chick embryos. We manipulated chondrocyte differentiation by supplementing these cultures either with BMP2, PTHrP and Sonic **hedgehog** as activators or with

Noggin and cyclopamine as **inhibitors** of the BMP and Ihh/PTHrP signaling systems. Overexpression of Ihh in the cartilage elements of transgenic mice results in an upregulation of PTHrP expression and a delayed onset of hypertrophic differentiation. Noggin treatment of limbs from these mice did not antagonize the effects of Ihh overexpression. Conversely, the promotion of chondrocyte maturation induced by cyclopamine, which blocks Ihh signaling, could not be rescued with BMP2. Thus BMP signaling does not act as a secondary signal of Ihh to induce PTHrP expression or to delay the onset of hypertrophic differentiation. Similar results were obtained using cultures of chick limbs. We further investigated the role of BMP signaling in regulating proliferation and hypertrophic differentiation of chondrocytes and identified three functions of BMP signaling in this process. First we found that maintaining a **normal** proliferation rate requires BMP and Ihh signaling acting in parallel. We further identified a role for BMP signaling in modulating the expression of Ihh. Finally, the application of Noggin to mouse limb explants resulted in advanced differentiation of terminally hypertrophic cells, implicating BMP signaling in delaying the process of hypertrophic differentiation itself. This role of BMP signaling is independent of the Ihh/PTHrP pathway.

RE.CNT 59 THERE ARE 59 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

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L4 ANSWER 27 OF 75 CAPLUS COPYRIGHT 2003 ACS on STN
AN 2001:886320 CAPLUS
DN 137:58414
TI Genetic evidence that Sil is required for the sonic hedgehog response pathway
AU Izraeli, Shai; Lowe, Linda A.; Bertness, Virginia L.; Campaner, Stefano;

Hahn, Heidi; Kirsch, Ilan R.; Kuehn, Michael R.
CS Genetics Branch, Center for Cancer Research, National Cancer Institute, NIH, Bethesda, MD, 20892-1360, USA
SO Genesis (New York, NY, United States) (2001), 31(2), 72-77
CODEN: GNESFY; ISSN: 1526-954X
PB Wiley-Liss, Inc.
DT Journal
LA English
AB The Sil gene encodes a cytosolic protein required for mouse embryonic midline and left/right axial development. Based on the phenotype of Sil mutant embryos, we hypothesized that Sil may be required for the activity of Sonic **Hedgehog** (Shh), a secreted signaling mol. also critically important for the development of the embryonic axes and found mutated in multiple types of cancer. Here we tested the genetic interaction between Sil and the Shh pathway by generating and analyzing embryos carrying mutations in both Sil and Patched (Ptch), a Shh receptor that **normally inhibits** the signaling pathway in the absence of ligand and when mutated leads to constitutive activation of the pathway. We find that Sil-/- Ptch-/- embryos do not activate the Shh pathway and instead have a phenotype indistinguishable from Sil-/- embryos, in which there is a loss of activity of Shh. These results provide genetic evidence that Sil is an essential component of the Shh response, acting downstream to Ptch.
RE.CNT 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD
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AB The Sil gene encodes a cytosolic protein required for mouse embryonic midline and left/right axial development. Based on the phenotype of Sil mutant embryos, we hypothesized that Sil may be required for the activity of Sonic **Hedgehog** (Shh), a secreted signaling mol. also critically important for the development of the embryonic axes and found mutated in multiple types of cancer. Here we tested the genetic interaction between Sil and the Shh pathway by generating and analyzing embryos carrying mutations in both Sil and Patched (Ptch), a Shh receptor that **normally inhibits** the signaling pathway in the absence of ligand and when mutated leads to constitutive activation of the pathway. We find that Sil-/- Ptch-/- embryos do not activate the Shh pathway and instead have a phenotype indistinguishable from Sil-/- embryos, in which there is a loss of activity of Shh. These results provide genetic evidence that Sil is an essential component of the Shh response, acting downstream to Ptch.

L4 ANSWER 28 OF 75 CAPLUS COPYRIGHT 2003 ACS on STN
AN 2001:815731 CAPLUS
DN 136:67162
TI Notch signalling and the initiation of neural development in the Drosophila eye
AU Baonza, Antonio; Freeman, Matthew
CS MRC Laboratory of Molecular Biology, Cambridge, CB2 2QH, UK
SO Development (Cambridge, United Kingdom) (2001), 128(20), 3889-3898
CODEN: DEVPED; ISSN: 0950-1991
PB Company of Biologists Ltd.
DT Journal
LA English
AB Neural detn. in the Drosophila eye occurs progressively. A diffusible signal, Dpp, causes undetd. cells first to adopt a "pre-proneural" state in which they are primed to start differentiating. A second signal is required to trigger the activation of the transcription factor Atonal, which causes the cells to initiate overt photoreceptor neuron differentiation. Both Dpp and the second signal are dependent on

Hedgehog (Hh) signaling. Previous work has shown that the Notch signaling pathway also has a proneural role in the eye (as well as a later, opposite function when it restricts the no. of cells becoming photoreceptors - a process of lateral **inhibition**). It is not clear how the early proneural role of Notch integrates with the other signaling pathways involved. The authors provide evidence that Notch activation by its ligand Delta is the second Hh-dependent signal required for neural detn. Notch activity **normally** only triggers Atonal expression in cells that have adopted the pre-proneural state induced by Dpp. The authors also report that Notch drives the transition from pre-proneural to proneural by downregulating two repressors of Atonal: Hairy and Extramacrochaetae.

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AB Neural detn. in the Drosophila eye occurs progressively. A diffusible signal, Dpp, causes undetd. cells first to adopt a "pre-proneural" state in which they are primed to start differentiating. A second signal is required to trigger the activation of the transcription factor Atonal, which causes the cells to initiate overt photoreceptor neuron differentiation. Both Dpp and the second signal are dependent on **Hedgehog** (Hh) signaling. Previous work has shown that the Notch signaling pathway also has a proneural role in the eye (as well as a later, opposite function when it restricts the no. of cells becoming photoreceptors - a process of lateral **inhibition**). It is not clear how the early proneural role of Notch integrates with the other signaling pathways involved. The authors provide evidence that Notch activation by its ligand Delta is the second Hh-dependent signal required for neural detn. Notch activity **normally** only triggers Atonal expression in cells that have adopted the pre-proneural state induced by Dpp. The authors also report that Notch drives the transition from pre-proneural to proneural by downregulating two repressors of Atonal: Hairy and Extramacrochaetae.

L4 ANSWER 29 OF 75 CAPLUS COPYRIGHT 2003 ACS on STN
AN 2001:777496 CAPLUS
Correction of: 1999:523933
DN 135:283833
Correction of: 131:267798
TI Gli proteins encode context-dependent positive and negative functions: implications for development and disease
AU Ruiz i Altaba, A.
CS The Skirball Institute, Developmental Genetics Program and Department of Cell Biology, NYU School of Medicine, New York, NY, 10016, USA
SO Development (Cambridge, United Kingdom) (1999), 126(14), 3205-3216
CODEN: DEVPED; ISSN: 0950-1991
PB Company of Biologists Ltd.
DT Journal
LA English
AB Several lines of evidence implicate zinc finger proteins of the Gli family in the final steps of **Hedgehog** signaling in **normal** development and disease. C-terminally truncated mutant GLI3 proteins are also assocd. with human syndromes, but it is not clear whether these C-terminally truncated Gli proteins fulfil the same function as full-length ones. Here, structure-function analyses of Gli proteins have been performed using floor plate and neuronal induction assays in frog embryos, as well as induction of alk. phosphatase (AP) in SHH-responsive mouse C3H10T1/2 cells. These assays show that C-terminal sequences are required for pos. inducing activity and cytoplasmic localization, whereas N-terminal sequences det. dominant neg. function and nuclear localization.

Analyses of nuclear targeted Gli1 and Gli2 proteins suggest that both activator and dominant neg. proteins are modified forms. In embryos and COS cells, tagged Gli cDNAs yield C-terminally deleted forms similar to that of Ci. These results thus provide a mol. basis for the human Polydactyly type A and Pallister-Hall Syndrome phenotypes, derived from the deregulated prodn. of C-terminally truncated GLI3 proteins. Analyses of full-length Gli function in 10T1/2 cells suggest that nuclear localization of activating forms is a regulated event and show that only Gli1 mimics SHH in inducing AP activity. Moreover, full-length Gli3 and all C-terminally truncated forms act antagonistically whereas Gli2 is inactive in this assay. In 10T1/2 cells, protein kinase A (PKA), a known **inhibitor** of Hh signaling, promotes Gli3 repressor formation and **inhibits** Gli1 function. Together, these findings suggest a context-dependent functional divergence of Gli protein function, in which a cell represses Gli3 and activates Gli1/2 prevents the formation of repressor Gli forms to respond to Shh. Interpretation of Hh signals by Gli proteins therefore appears to involve a fine balance of divergent functions within each and among different Gli proteins, the misregulation of which has profound biol. consequences.

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AB Several lines of evidence implicate zinc finger proteins of the Gli family in the final steps of **Hedgehog** signaling in **normal** development and disease. C-terminally truncated mutant GLI3 proteins are also assocd. with human syndromes, but it is not clear whether these C-terminally truncated Gli proteins fulfil the same function as full-length ones. Here, structure-function analyses of Gli proteins have been performed using floor plate and neuronal induction assays in frog embryos, as well as induction of alk. phosphatase (AP) in SHH-responsive mouse C3H10T1/2 cells. These assays show that C-terminal sequences are required for pos. inducing activity and cytoplasmic localization, whereas N-terminal sequences det. dominant neg. function and nuclear localization. Analyses of nuclear targeted Gli1 and Gli2 proteins suggest that both activator and dominant neg. proteins are modified forms. In embryos and COS cells, tagged Gli cDNAs yield C-terminally deleted forms similar to that of Ci. These results thus provide a mol. basis for the human Polydactyly type A and Pallister-Hall Syndrome phenotypes, derived from the deregulated prodn. of C-terminally truncated GLI3 proteins. Analyses of full-length Gli function in 10T1/2 cells suggest that nuclear localization of activating forms is a regulated event and show that only Gli1 mimics SHH in inducing AP activity. Moreover, full-length Gli3 and all C-terminally truncated forms act antagonistically whereas Gli2 is inactive in this assay. In 10T1/2 cells, protein kinase A (PKA), a known **inhibitor** of Hh signaling, promotes Gli3 repressor formation and **inhibits** Gli1 function. Together, these findings suggest a context-dependent functional divergence of Gli protein function, in which a cell represses Gli3 and activates Gli1/2 prevents the formation of repressor Gli forms to respond to Shh. Interpretation of Hh signals by Gli proteins therefore appears to involve a fine balance of divergent functions within each and among different Gli proteins, the misregulation of which has profound biol. consequences.

L4 ANSWER 30 OF 75 CAPLUS COPYRIGHT 2003 ACS on STN
AN 2001:747593 CAPLUS
DN 135:283224
TI Small organic molecule hedgehog agonists as regulators of cell proliferation and differentiation
IN Baxter, Anthony David; Boyd, Edward Andrew; Guicherit, Oivin M.; Porter, Jeffrey; Price, Stephen; Rubin, Lee E.

PA Curis, Inc., USA
SO PCT Int. Appl., 246 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 3

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001074344	A2	20011011	WO 2001-US10296	20010330
	WO 2001074344	A3	20020523		
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	US 6613798	B1	20030902	US 2000-724955	20001128
	EP 1272168	A2	20030108	EP 2001-922914	20010330
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
	US 2003139457	A1	20030724	US 2002-245844	20020917
PRAI	US 2000-193279P	P	20000330		
	US 2000-724492	A	20001128		
	US 2000-724955	A	20001128		
	WO 2001-US10296	W	20010330		
	US 2001-964276	A2	20010926		

OS MARPAT 135:283224
AB Methods and reagents are provided for modulating proliferation or differentiation in a cell or tissue, comprising contacting the cell with a **hedgehog** agonist. In certain embodiments, the methods and reagents may be employed to correct or **inhibit** an aberrant or unwanted growth state, e.g., by antagonizing a **normal** ptc pathway or agonizing smoothened or **hedgehog** activity. Prepn. of compds. (e.g. I) is described.
AB Methods and reagents are provided for modulating proliferation or differentiation in a cell or tissue, comprising contacting the cell with a **hedgehog** agonist. In certain embodiments, the methods and reagents may be employed to correct or **inhibit** an aberrant or unwanted growth state, e.g., by antagonizing a **normal** ptc pathway or agonizing smoothened or **hedgehog** activity. Prepn. of compds. (e.g. I) is described.

L4 ANSWER 31 OF 75 CAPLUS COPYRIGHT 2003 ACS on STN
AN 2001:670813 CAPLUS
DN 135:316117
TI Wnt signaling and PKA control Nodal expression and left-right determination in the chick embryo
AU Rodriguez-Esteban, Concepcion; Capdevila, Javier; Kawakami, Yasuhiko; Belmonte, Juan Carlos Izpisua
CS Gene Expression Laboratory, The Salk Institute for Biological Studies, La Jolla, CA, 92037, USA
SO Development (Cambridge, United Kingdom) (2001), 128(16), 3189-3195
CODEN: DEVPED; ISSN: 0950-1991
PB Company of Biologists Ltd.
DT Journal
LA English

AB Expression of the Nodal gene, which encodes a member of the TGF.beta. superfamily of secreted factors, localizes to the left side of the developing embryo in all vertebrates examd. so far. This asym. pattern correlates with **normal** development of the left-right axis. The authors now show that the Wnt and PKA signaling pathways control left-right detn. in the chick embryo through Nodal. A Wnt/.beta.-catenin pathway controls Nodal expression in and around Hensen's node, without affecting the upstream regulators Sonic **hedgehog**, Car and Fibroblast Growth Factor 8. Transcription of Nodal is also pos. regulated by a protein kinase A-dependent pathway. Both the adhesion protein N-cadherin and PKI (an endogenous protein kinase A **inhibitor**) are localized to the right side of the node and may contribute to restrict Nodal activation by Wnt signaling and PKA to the left side of the node.

RE.CNT 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

AB Expression of the Nodal gene, which encodes a member of the TGF.beta. superfamily of secreted factors, localizes to the left side of the developing embryo in all vertebrates examd. so far. This asym. pattern correlates with **normal** development of the left-right axis. The authors now show that the Wnt and PKA signaling pathways control left-right detn. in the chick embryo through Nodal. A Wnt/.beta.-catenin pathway controls Nodal expression in and around Hensen's node, without affecting the upstream regulators Sonic **hedgehog**, Car and Fibroblast Growth Factor 8. Transcription of Nodal is also pos. regulated by a protein kinase A-dependent pathway. Both the adhesion protein N-cadherin and PKI (an endogenous protein kinase A **inhibitor**) are localized to the right side of the node and may contribute to restrict Nodal activation by Wnt signaling and PKA to the left side of the node.

L4 ANSWER 32 OF 75 CAPLUS COPYRIGHT 2003 ACS on STN
AN 2001:611887 CAPLUS
DN 135:150180
TI Wnt signals are targets and mediators of Gli function
AU Mullor, Jose L.; Dahmane, Nadia; Sun, Tao; Ruiz i Altaba, Ariel
CS The Skirball Institute, Developmental Genetics Program and Department of Cell Biology, NYU School of Medicine, New York, NY, 10016, USA
SO Current Biology (2001), 11(10), 769-773
CODEN: CUBLE2; ISSN: 0960-9822
PB Cell Press
DT Journal
LA English
AB There is growing evidence that Gli proteins participate in the mediation of **Hedgehog** and FGF signaling in neural and mesodermal development. However, little is known about which genes act downstream of Gli proteins. Here we show the regulation of members of the Wnt family by Gli proteins in different contexts. Our findings indicate that Gli2 regulates Wnt8 expression in the ventral marginal zone of the early frog embryo: activating Gli2 constructs induce ectopic Wnt8 expression in animal cap explants, whereas repressor forms **inhibit** its endogenous expression in the marginal zone. Using truncated Frizzled and dominant-neg. Wnt constructs, we then show the requirement of at least two Wnt proteins, Wnt8 and Wnt11, for Gli2/3-induced posterior mesodermal development. Blocking Wnt signals, however, **inhibits** Gli2/3-induced morphogenesis, but not mesodermal specification. Gli2/3 may therefore **normally** coordinate the action of these two Wnt proteins, which regulate distinct downstream pathways. In addn., the finding that Gli1 consistently induces a distinct set of Wnt genes in animal cap explants and in skin tumors suggests that Wnt regulation by Gli proteins is general. Such a mechanism may link signals that induce Gli

activity, such as FGFs and **Hedgehogs**, with Wnt function.

AB There is growing evidence that Gli proteins participate in the mediation of **Hedgehog** and FGF signaling in neural and mesodermal development. However, little is known about which genes act downstream of Gli proteins. Here we show the regulation of members of the Wnt family by Gli proteins in different contexts. Our findings indicate that Gli2 regulates Wnt8 expression in the ventral marginal zone of the early frog embryo: activating Gli2 constructs induce ectopic Wnt8 expression in animal cap explants, whereas repressor forms **inhibit** its endogenous expression in the marginal zone. Using truncated Frizzled and dominant-neg. Wnt constructs, we then show the requirement of at least two Wnt proteins, Wnt8 and Wnt11, for Gli2/3-induced posterior mesodermal development. Blocking Wnt signals, however, **inhibits** Gli2/3-induced morphogenesis, but not mesodermal specification. Gli2/3 may therefore **normally** coordinate the action of these two Wnt proteins, which regulate distinct downstream pathways. In addn., the finding that Gli1 consistently induces a distinct set of Wnt genes in animal cap explants and in skin tumors suggests that Wnt regulation by Gli proteins is general. Such a mechanism may link signals that induce Gli activity, such as FGFs and **Hedgehogs**, with Wnt function.

L4 ANSWER 33 OF 75 CAPLUS COPYRIGHT 2003 ACS on STN
AN 2001:379401 CAPLUS
DN 135:105484
TI Patched1 interacts with cyclin B1 to regulate cell cycle progression
AU Barnes, Elizabeth A.; Kong, Monica; Ollendorff, Vincent; Donoghue, Daniel J.
CS Department of Chemistry and Biochemistry, Center for Molecular Genetics, University of California, San Diego, La Jolla, CA, 92093-0367, USA
SO EMBO Journal (2001), 20(9), 2214-2223
CODEN: EMJODG; ISSN: 0261-4189
PB Oxford University Press
DT Journal
LA English
AB The initiation of mitosis requires the activation of M-phase promoting factor (MPF). MPF activation and its subcellular localization are dependent on the phosphorylation state of its components, cdc2 and cyclin B1. In a two-hybrid screen using a bait protein to mimic phosphorylated cyclin B1, we identified a novel interaction between cyclin B1 and patched1 (ptc1), a tumor suppressor assocd. with basal cell carcinoma (BCC). Ptc1 interacted specifically with constitutively phosphorylated cyclin B1 derivs. and was able to alter their **normal** subcellular localization. Furthermore, addn. of the ptc1 ligand, sonic **hedgehog** (shh), disrupts this interaction and allows cyclin B1 to localize to the nucleus. Expression of ptc1 in 293T cells was **inhibitory** to cell proliferation; this **inhibition** could be relieved by coexpression of a cyclin B1 deriv. that constitutively localizes to the nucleus and that could not interact with ptc1 due to phosphorylation-site mutations to Ala. In addn., we demonstrate that endogenous ptc1 and endogenous cyclin B1 interact in vivo. The findings reported here demonstrate that ptc1 participates in detg. the subcellular localization of cyclin B1 and suggest a link between the tumor suppressor activity of ptc1 and the regulation of cell division. Thus, we propose that ptc1 participates in a G2/M checkpoint by regulating the localization of MPF.
RE.CNT 46 THERE ARE 46 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT
AB The initiation of mitosis requires the activation of M-phase promoting factor (MPF). MPF activation and its subcellular localization are

dependent on the phosphorylation state of its components, cdc2 and cyclin B1. In a two-hybrid screen using a bait protein to mimic phosphorylated cyclin B1, we identified a novel interaction between cyclin B1 and patched1 (ptc1), a tumor suppressor assocd. with basal cell carcinoma (BCC). Ptc1 interacted specifically with constitutively phosphorylated cyclin B1 derivs. and was able to alter their **normal** subcellular localization. Furthermore, addn. of the ptc1 ligand, sonic **hedgehog** (shh), disrupts this interaction and allows cyclin B1 to localize to the nucleus. Expression of ptc1 in 293T cells was **inhibitory** to cell proliferation; this **inhibition** could be relieved by coexpression of a cyclin B1 deriv. that constitutively localizes to the nucleus and that could not interact with ptc1 due to phosphorylation-site mutations to Ala. In addn., we demonstrate that endogenous ptc1 and endogenous cyclin B1 interact in vivo. The findings reported here demonstrate that ptc1 participates in detg. the subcellular localization of cyclin B1 and suggest a link between the tumor suppressor activity of ptc1 and the regulation of cell division. Thus, we propose that ptc1 participates in a G2/M checkpoint by regulating the localization of MPF.

L4 ANSWER 34 OF 75 CAPLUS COPYRIGHT 2003 ACS on STN
AN 2001:350476 CAPLUS
DN 135:41182
TI Effect of thyroliberin on motor and autonomous components of conditional reflexes in the monkey Macaca mulatta
AU Sollertinskaya, T. N.; Grigor'yan, R. A.
CS Sechenov Institute of Evolutionary Physiology and Biochemistry, Russian Academy of Sciences, St. Petersburg, Russia
SO Journal of Evolutionary Biochemistry and Physiology (Translation of Zhurnal Evolyutsionnoi Biokhimii i Fiziologii) (2000), 36(5), 583-587
CODEN: JEBPA9; ISSN: 0022-0930
PB MAIK Nauka/Interperiodica Publishing
DT Journal
LA English
AB The effect of thyroliberin (35-40 .mu.g/kg) on the conditional reflex activity of monkeys was studied on the model of feeding behavior in a primatol. chair. It has been established that s.c. injection of thyroliberin to monkeys has an activating effect on the conditional reflex activity for 5-7 days, although the effect is more pronounced during the first days after injection of the prepn. Injection of thyroliberin is accompanied by shortening of the latent period of the conditional instrumental reflex (down to 1-2 s, while the **normal** value is 3-5 s), a decrease of the rate of respiratory movements down to 35-40 per 1 min (while the **normal** value is 65-80 per 1 min). Injection of thyroliberin at the same doses is accompanied by disinhibition of the differential **inhibition** and facilitation of formation of extinctive **inhibition**. Comparison of the data obtained with similar results on lower mammals (**hedgehogs**, rabbits) indicates the thyroliberin effect in monkeys to be more pronounced with respect to conditional forms of the nervous activity than to unconditional ones-orienting reaction, motor activity.
RE.CNT 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT
AB The effect of thyroliberin (35-40 .mu.g/kg) on the conditional reflex activity of monkeys was studied on the model of feeding behavior in a primatol. chair. It has been established that s.c. injection of thyroliberin to monkeys has an activating effect on the conditional reflex activity for 5-7 days, although the effect is more pronounced during the first days after injection of the prepn. Injection of thyroliberin is

accompanied by shortening of the latent period of the conditional instrumental reflex (down to 1-2 s, while the **normal** value is 3-5 s), a decrease of the rate of respiratory movements down to 35-40 per 1 min (while the **normal** value is 65-80 per 1 min). Injection of thyroliberin at the same doses is accompanied by disinhibition of the differential **inhibition** and facilitation of formation of extinctive **inhibition**. Comparison of the data obtained with similar results on lower mammals (**hedgehogs**, rabbits) indicates the thyroliberin effect in monkeys to be more pronounced with respect to conditional forms of the nervous activity than to unconditional ones-orienting reaction, motor activity.

L4 ANSWER 35 OF 75 CAPLUS COPYRIGHT 2003 ACS on STN
AN 2001:283777 CAPLUS
DN 134:311102
TI Preparation and formulation of heterocycles as mediators of hedgehog signaling pathways for pharmaceutical and cosmetic uses
IN Baxter, Anthony David; Boyd, Edward Andrew; Guicherit, Oivin M.; Price, Stephen; Rubin, Lee
PA Curis, Inc., USA
SO PCT Int. Appl., 219 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 4

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001026644	A2	20010419	WO 2000-US28579	20001013
	WO 2001026644	A3	20020418		
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	EP 1227805	A2	20020807	EP 2000-978225	20001013
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				
	JP 2003511411	T2	20030325	JP 2001-529434	20001013
	US 6552016	B1	20030422	US 2000-688018	20001013
PRAI	US 1999-159417P	P	19991014		
	US 2000-196543P	P	20000411		
	US 2000-211919P	P	20000616		
	US 2000-240536P	P	20001013		
	WO 2000-US28579	W	20001013		

OS MARPAT 134:311102
AB Heterocycles, such as I [E = O, S, NR; D, X = NR2, O, S, bond, etc.; L = linking group, such as alkylene, alkenylene, alkynylene; XL = piperazin-1,4-diyl, etc.; R, R1, R2 = H, alkyl, acyl, arylalkyl, heteroarylalkyl, etc.], were prepd. for pharmaceutical and cosmetic use. Thus, pyrrolidine II was prepd. via a multistep synthetic sequence which started with trans-4-hydroxy-L-proline, 3-methoxybenzaldehyde, piperonal, tert-butylacetyl chloride, and N-(tert-butoxycarbonyl)piperazine. The prepd. pyrrolidines were tested for agonist activity for **inhibiting** aberrant growth states resulting from **hedgehog** gain-of-function, ptc loss-of-function or smoothened gain-of-function

comprising contacting the cell with a **hedgehog** antagonist, such as a small mol., in a sufficient amt. to aberrant growth state, e.g., to agonize a **normal** ptc pathway or antagonize smoothened or **hedgehog** activity.

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L4 ANSWER 36 OF 75 CAPLUS COPYRIGHT 2003 ACS on STN
AN 2001:272992 CAPLUS
DN 134:364339
TI Regulation of retinal ganglion cell production by Sonic hedgehog
AU Zhang, Xiang-Mei; Yang, Xian-Jie
CS Department of Ophthalmology, Jules Stein Eye Institute, Molecular Biology Institute, UCLA School of Medicine, Los Angeles, CA, 90095, USA
SO Development (Cambridge, United Kingdom) (2001), 128(6), 943-957
CODEN: DEVPED; ISSN: 0950-1991
PB Company of Biologists Ltd.
DT Journal
LA English
AB Previous work has shown that prodn. of retinal ganglion cells is in part regulated by **inhibitory** factors secreted by ganglion cell themselves; however, the identities of these mols. are not known. Recent studies have demonstrated that the signaling mol. Sonic **hedgehog** (Shh) secreted by differentiated retinal ganglion cells is required to promote the progression of ganglion cell differentiation wave front and to induce its own expression. The authors present evidence that Shh signals play a role to neg. regulate ganglion cell genesis behind the differentiation wave front. Higher levels of Shh expression are detected behind the wave front as ganglion cells accumulate, while the Patched 1 receptor of Shh is expressed in adjacent retinal progenitor cells. Retroviral-mediated overexpression of Shh results in reduced ganglion cell proportions in vivo and in vitro. Conversely, **inhibiting** endogenous Shh activity by anti-Shh antibodies leads to an increased prodn. of ganglion cells. Shh signals modulate ganglion cell prodn. within the **normal** period of ganglion cell genesis in vitro without significantly affecting cell proliferation or cell death. Moreover, Shh signaling affects progenitor cell specification towards the ganglion cell fate during or soon after their last mitotic cycle. Thus, Shh derived from differentiated ganglion cells serves as a neg. regulator behind the differentiation wave front to control ganglion cell genesis from the competent progenitor pool. Based on these results and other recent findings, the authors propose that Shh signals secreted by early-differentiated retinal neurons play dual roles at distinct concn. thresholds to orchestrate the progression of retinal neurogenic wave and the emergence of new neurons.
RE.CNT 102 THERE ARE 102 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

AB Previous work has shown that prodn. of retinal ganglion cells is in part regulated by **inhibitory** factors secreted by ganglion cell themselves; however, the identities of these mols. are not known. Recent studies have demonstrated that the signaling mol. Sonic **hedgehog** (Shh) secreted by differentiated retinal ganglion cells is required to promote the progression of ganglion cell differentiation wave front and to induce its own expression. The authors present evidence that Shh signals play a role to neg. regulate ganglion cell genesis behind the differentiation wave front. Higher levels of Shh expression are detected behind the wave front as ganglion cells accumulate, while the Patched 1 receptor of Shh is expressed in adjacent retinal progenitor cells. Retroviral-mediated overexpression of Shh results in reduced ganglion cell proportions in vivo and in vitro. Conversely, **inhibiting** endogenous Shh activity by anti-Shh antibodies leads to an increased prodn. of ganglion cells. Shh signals modulate ganglion cell prodn. within the **normal** period of ganglion cell genesis in vitro without significantly affecting cell proliferation or cell death. Moreover, Shh signaling affects progenitor cell specification towards the ganglion cell fate during or soon after their last mitotic cycle. Thus, Shh derived from differentiated ganglion cells serves as a neg. regulator behind the differentiation wave front to control ganglion cell genesis from the competent progenitor pool. Based on these results and other recent findings, the authors propose that Shh signals secreted by early-differentiated retinal neurons play dual roles at distinct concn. thresholds to orchestrate the progression of retinal neurogenic wave and the emergence of new neurons.

L4 ANSWER 37 OF 75 CAPLUS COPYRIGHT 2003 ACS on STN
AN 2001:153540 CAPLUS
DN 134:348436
TI Hedgehog signaling regulation of homeodomain protein islet duodenum homeobox-1 expression in pancreatic .beta.-cells
AU Thomas, Melissa K.; Lee, Jee H.; Rastalsky, Naina; Habener, Joel F.
CS Laboratory of Molecular Endocrinology, Harvard Medical School, Massachusetts General Hospital, Boston, MA, 02114, USA
SO Endocrinology (2001), 142(3), 1033-1040
CODEN: ENDOAO; ISSN: 0013-7227
PB Endocrine Society
DT Journal
LA English
AB Insulin gene expression in pancreatic .beta.-cells is regulated by signals from developmental morphogen proteins known as **hedgehogs** (Hhs). By analyzing 5'-deletion insulin promoter-reporter constructs in transient transfections of clonal INS-1 .beta.-cells, we located activating Hh-responsive regions within the rat insulin I promoter that include the glucose-response elements Far (E2) and Flat (A2/A3). Activation of Hh signaling in INS-1 cells by ectopic Hh expression increased (and **inhibition** of Hh signaling with the Hh-specific **inhibitor** cyclopamine decreased) transcriptional activation of a multimerized FarFlat enhancer-reporter construct. In DNA-binding studies, nuclear exts. from INS-1 cells activated by ectopic Hh expression increased (and exts. from INS-1 cells treated with cyclopamine decreased) protein binding to a radiolabeled FarFlat oligonucleotide probe. An antiserum directed against the transcription factor islet duodenum homeobox-1 (IDX-1), a regulator of pancreas development and activator of the insulin gene promoter, attenuated the binding activity of Hh-responsive protein complexes. Nuclear IDX-1 protein levels on Western blots were increased by ectopic Hh expression, thereby providing a mechanism for Hh-mediated regulation of the insulin promoter. Addn. of cyclopamine to INS-1 cells

decreased IDX-1 mRNA expression. In transient transfections of a -4.5-kb mouse IDX-1 promoter-reporter construct, ectopic Hh expression increased (and cyclopamine administration decreased) transcriptional activation of the IDX-1 promoter in a dose-dependent manner. Thus, the IDX-1 gene is a direct regulatory target of Hh signaling in insulin-producing pancreatic .beta.-cells. We propose that Hh signaling activates the insulin gene promoter indirectly via the direct activation of IDX-1 expression. Because IDX-1 gene expression is essential for insulin gene expression, pancreatic .beta.-cells development, and **normal** glucose homeostasis, our findings that Hh signaling regulates IDX-1 expression in the endocrine pancreas suggest possible novel therapeutic approaches for diabetes mellitus.

RE.CNT 67 THERE ARE 67 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

AB Insulin gene expression in pancreatic .beta.-cells is regulated by signals from developmental morphogen proteins known as **hedgehogs** (Hhs). By analyzing 5'-deletion insulin promoter-reporter constructs in transient transfections of clonal INS-1 .beta.-cells, we located activating Hh-responsive regions within the rat insulin I promoter that include the glucose-response elements Far (E2) and Flat (A2/A3). Activation of Hh signaling in INS-1 cells by ectopic Hh expression increased (and **inhibition** of Hh signaling with the Hh-specific **inhibitor** cyclopamine decreased) transcriptional activation of a multimerized FarFlat enhancer-reporter construct. In DNA-binding studies, nuclear exts. from INS-1 cells activated by ectopic Hh expression increased (and exts. from INS-1 cells treated with cyclopamine decreased) protein binding to a radiolabeled FarFlat oligonucleotide probe. An antiserum directed against the transcription factor islet duodenum homeobox-1 (IDX-1), a regulator of pancreas development and activator of the insulin gene promoter, attenuated the binding activity of Hh-responsive protein complexes. Nuclear IDX-1 protein levels on Western blots were increased by ectopic Hh expression, thereby providing a mechanism for Hh-mediated regulation of the insulin promoter. Addn. of cyclopamine to INS-1 cells decreased IDX-1 mRNA expression. In transient transfections of a -4.5-kb mouse IDX-1 promoter-reporter construct, ectopic Hh expression increased (and cyclopamine administration decreased) transcriptional activation of the IDX-1 promoter in a dose-dependent manner. Thus, the IDX-1 gene is a direct regulatory target of Hh signaling in insulin-producing pancreatic .beta.-cells. We propose that Hh signaling activates the insulin gene promoter indirectly via the direct activation of IDX-1 expression. Because IDX-1 gene expression is essential for insulin gene expression, pancreatic .beta.-cells development, and **normal** glucose homeostasis, our findings that Hh signaling regulates IDX-1 expression in the endocrine pancreas suggest possible novel therapeutic approaches for diabetes mellitus.

L4 ANSWER 38 OF 75 CAPLUS COPYRIGHT 2003 ACS on STN
AN 2001:120344 CAPLUS
DN 134:250012
TI Expression of Sonic Hedgehog downstream genes is modified in rat embryos exposed in utero to a distal inhibitor of cholesterol biosynthesis
AU Gofflot, Francoise; Gaoua, Wassila; Bourguignon, Loic; Roux, Charles; Picard, Jacques J.
CS Unit of Developmental Genetics, Universite Catholique de Louvain, Brussels, B-1200, Belg.
SO Developmental Dynamics (2001), 220(2), 99-111
CODEN: DEDYEI; ISSN: 1058-8388
PB Wiley-Liss, Inc.
DT Journal

LA English
AB Holoprosencephaly is a common developmental anomaly of the forebrain and midface, that has been assocd. with mutations in the Sonic **Hedgehog** gene, and with perturbations of cholesterol synthesis and metab. in mammalian embryos. The study presented here was aimed to evaluate the functional relationship between these two causal agents in the genesis of the phenotype. Therefore, we used rat embryos exposed in utero to a distal **inhibitor** of cholesterol biosynthesis (AY9944) in which we analyzed different Shh-dependent processes, as evaluated by the expression of eight target genes. In addn., to delineate between the impact of cholesterol shortage and/or sterol precursors accumulation on the Shh signaling cascade we exposed rat embryos to AY9944 and we provided complementary diets rich in cholesterol and 7-DHC. At the early-somite stage we obsd. a redn. of Shh signaling in AY9944 treated embryos, resulting in the definition of a narrower ventral domain. Later in development this redn. of Shh signaling led to a complete interruption of the pathway in the rostral hindbrain and caudal midbrain. Other regions such as the forebrain and the spinal cord appeared less sensitive to the redn. of Shh signaling and interruption of the pathway was only obsd. in a subset of embryos. Finally, we did provide evidence that 7-DHC accumulation is compatible with **normal** activity of Shh, as long as cholesterol levels in embryonic tissue is sufficient.
RE.CNT 68 THERE ARE 68 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT
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L4 ANSWER 39 OF 75 CAPLUS COPYRIGHT 2003 ACS on STN
AN 2000:908355 CAPLUS
DN 134:234587
TI Downregulation of Hedgehog signaling is required for organogenesis of the small intestine in Xenopus
AU Zhang, Jian; Rosenthal, Arnon; de Sauvage, Frederic J.; Shivdasani, Ramesh A.
CS Department of Molecular Oncology, Genentech, Inc., South San Francisco, CA, 94080, USA
SO Developmental Biology (Orlando, FL, United States) (2001), 229(1), 188-202
CODEN: DEBIAO; ISSN: 0012-1606
PB Academic Press
DT Journal

LA English
AB **Hedgehog** ligands interact with receptor complexes contg. Patched (PTC) and Smoothened (SMO) proteins to regulate many aspects of development. The mutation W535L (SmoM2) in human Smo is assocd. with basal cell skin cancers, causes constitutive, ligand-independent signaling through the **Hedgehog** pathway, and provides a powerful means to test effects of unregulated **Hedgehog** signaling. Expression of SmoM2 in Xenopus embryos leads to developmental anomalies that are consistent with known requirements for regulated **Hedgehog** signaling in the eye and pancreas. Addnl., it results in failure of midgut epithelial cytodifferentiation and of the intestine to lengthen and coil. The midgut mesenchyme shows increased cell nos. and attenuated expression of the differentiation marker smooth muscle actin. With the exception of the pancreas, differentiation of foregut and hindgut derivs. is unaffected. The intestinal epithelial abnormalities are reproduced in embryos or organ explants treated directly with active recombinant **hedgehog** protein. Ptc mRNA, a principal target of **Hedgehog** signaling, is maximally expressed at stages corresponding to the onset of the intestinal defects. In advanced embryos expressing SmoM2, Ptc expression is remarkably confined to the intestinal wall. Considered together, these findings suggest that the splanchnic mesoderm responds to endodermal **Hedgehog** signals by **inhibiting** the transition of midgut endoderm into intestinal epithelium and that attenuation of this feedback is required for **normal** development of the vertebrate intestine. (c) 2001 Academic Press.
RE.CNT 69 THERE ARE 69 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT
AB **Hedgehog** ligands interact with receptor complexes contg. Patched (PTC) and Smoothened (SMO) proteins to regulate many aspects of development. The mutation W535L (SmoM2) in human Smo is assocd. with basal cell skin cancers, causes constitutive, ligand-independent signaling through the **Hedgehog** pathway, and provides a powerful means to test effects of unregulated **Hedgehog** signaling. Expression of SmoM2 in Xenopus embryos leads to developmental anomalies that are consistent with known requirements for regulated **Hedgehog** signaling in the eye and pancreas. Addnl., it results in failure of midgut epithelial cytodifferentiation and of the intestine to lengthen and coil. The midgut mesenchyme shows increased cell nos. and attenuated expression of the differentiation marker smooth muscle actin. With the exception of the pancreas, differentiation of foregut and hindgut derivs. is unaffected. The intestinal epithelial abnormalities are reproduced in embryos or organ explants treated directly with active recombinant **hedgehog** protein. Ptc mRNA, a principal target of **Hedgehog** signaling, is maximally expressed at stages corresponding to the onset of the intestinal defects. In advanced embryos expressing SmoM2, Ptc expression is remarkably confined to the intestinal wall. Considered together, these findings suggest that the splanchnic mesoderm responds to endodermal **Hedgehog** signals by **inhibiting** the transition of midgut endoderm into intestinal epithelium and that attenuation of this feedback is required for **normal** development of the vertebrate intestine. (c) 2001 Academic Press.

L4 ANSWER 40 OF 75 CAPLUS COPYRIGHT 2003 ACS on STN
AN 2000:880221 CAPLUS
DN 134:142103
TI Thyroid hormones regulate hypertrophic chondrocyte differentiation and expression of parathyroid hormone-related peptide and its receptor during endochondral bone formation
AU Stevens, David A.; Hasserjian, Robert P.; Robson, Helen; Siebler, Thomas;

Shalet, Stephen M.; Williams, Graham R.
CS Imperial College School of Medicine Molecular Endocrinology Group, Division of Medicine and Medical Research Council Clinical Sciences Center, Imperial College School of Medicine, Hammersmith Hospital, London, UK
SO Journal of Bone and Mineral Research (2000), 15(12), 2431-2442
CODEN: JBMREJ; ISSN: 0884-0431
PB American Society for Bone and Mineral Research
DT Journal
LA English
AB Hypothyroidism in children causes developmental abnormalities in bone and growth arrest, while thyrotoxicosis accelerates growth rate and advances bone age. To det. the effects of thyroid hormones on endochondral bone formation, the authors examd. epiphyseal growth plates in control, hypothyroid, thyrotoxic, and hypothyroid-thyroxine (hypo-T4)-treated rats. Hypothyroid growth plates were grossly disorganized, contained an abnormal matrix rich in heparan sulfate, and hypertrophic chondrocyte differentiation failed to progress. These effects correlated with the absence of collagen X expression and increased parathyroid hormone-related protein (PTHrP) mRNA expression. In thyrotoxic growth plates, histol. essentially was **normal** but PTHrP receptor (PTHrP-R) mRNA was undetectable. PTHrP is a potent **inhibitor** of hypertrophic chondrocyte differentiation that acts in a neg. feedback loop with the secreted factor Indian **hedgehog** (Ihh) to regulate endochondral bone formation. Thyroid hormone receptor .alpha.1(TR.alpha.1), TR.alpha.2, and TR.beta.1 proteins were localized to reserve zone progenitor cells and proliferating chondrocytes in euthyroid rat cartilage; regions in which PTHrP and PTHrP-R expression were affected by thyroid status. Thus, dysregulated Ihh/PTHrP feedback loop activity may be a key mechanism that underlies growth disorders in childhood thyroid disease.
RE.CNT 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT
AB Hypothyroidism in children causes developmental abnormalities in bone and growth arrest, while thyrotoxicosis accelerates growth rate and advances bone age. To det. the effects of thyroid hormones on endochondral bone formation, the authors examd. epiphyseal growth plates in control, hypothyroid, thyrotoxic, and hypothyroid-thyroxine (hypo-T4)-treated rats. Hypothyroid growth plates were grossly disorganized, contained an abnormal matrix rich in heparan sulfate, and hypertrophic chondrocyte differentiation failed to progress. These effects correlated with the absence of collagen X expression and increased parathyroid hormone-related protein (PTHrP) mRNA expression. In thyrotoxic growth plates, histol. essentially was **normal** but PTHrP receptor (PTHrP-R) mRNA was undetectable. PTHrP is a potent **inhibitor** of hypertrophic chondrocyte differentiation that acts in a neg. feedback loop with the secreted factor Indian **hedgehog** (Ihh) to regulate endochondral bone formation. Thyroid hormone receptor .alpha.1(TR.alpha.1), TR.alpha.2, and TR.beta.1 proteins were localized to reserve zone progenitor cells and proliferating chondrocytes in euthyroid rat cartilage; regions in which PTHrP and PTHrP-R expression were affected by thyroid status. Thus, dysregulated Ihh/PTHrP feedback loop activity may be a key mechanism that underlies growth disorders in childhood thyroid disease.

L4 ANSWER 41 OF 75 CAPLUS COPYRIGHT 2003 ACS on STN
AN 2000:763231 CAPLUS
DN 134:51125
TI Regulation of Gli activity by all-trans retinoic acid in mouse

keratinocytes
AU Goyette, Philippe; Allan, Deborah; Peschard, Pascal; Chen, Chang Feng; Wang, Wei; Lohnes, David
CS The Institut de Recherches Cliniques de Montreal, Montreal, QC, H2W 1R7, Can.
SO Cancer Research (2000), 60(19), 5386-5389
CODEN: CNREA8; ISSN: 0008-5472
PB American Association for Cancer Research
DT Journal
LA English
AB Sonic **hedgehog** (Shh) signaling is essential for many **normal** developmental processes. The Shh signal is interpreted by the Gli transcription factors. Elevated Gli-1 expression has been assocd. with several neoplasms, including basal cell carcinoma. All-trans retinoic acid (RA) has strong effects on epidermal growth and differentiation and has been used for the treatment of various epithelial disorders. In this report, the authors show that RA can **inhibit** Gli activity in immortalized murine keratinocytes in a RA receptor-specific manner. This **inhibition** may occur, at least in part, through sequestration of the transcriptional coactivator cAMP-responsive element-binding protein-binding protein and suggests a novel effect of retinoid excess on Shh signaling.
RE.CNT 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT
AB Sonic **hedgehog** (Shh) signaling is essential for many **normal** developmental processes. The Shh signal is interpreted by the Gli transcription factors. Elevated Gli-1 expression has been assocd. with several neoplasms, including basal cell carcinoma. All-trans retinoic acid (RA) has strong effects on epidermal growth and differentiation and has been used for the treatment of various epithelial disorders. In this report, the authors show that RA can **inhibit** Gli activity in immortalized murine keratinocytes in a RA receptor-specific manner. This **inhibition** may occur, at least in part, through sequestration of the transcriptional coactivator cAMP-responsive element-binding protein-binding protein and suggests a novel effect of retinoid excess on Shh signaling.

L4 ANSWER 42 OF 75 CAPLUS COPYRIGHT 2003 ACS on STN
AN 2000:627748 CAPLUS
DN 133:307924
TI Smoothened activates G.alpha.i-mediated signaling in frog melanophores
AU DeCamp, Dianne L.; Thompson, Teresa M.; De Sauvage, Frederic J.; Lerner, Michael R.
CS Department of Pharmacology, The University of Texas Southwestern Medical Center, Dallas, TX, 75390-9069, USA
SO Journal of Biological Chemistry (2000), 275(34), 26322-26327
CODEN: JBCHA3; ISSN: 0021-9258
PB American Society for Biochemistry and Molecular Biology
DT Journal
LA English
AB The 7-pass transmembrane protein Smoothened was investigated for its ability to act as a G-protein-coupled receptor in Xenopus laevis melanophores. A plasmid contg. the human Smoothened cDNA insert was transfected into immortalized frog pigment cells. Cells expressing the protein showed a phenotype of persistent pigment aggregation, a hallmark of constitutive G.alpha.i activation. Smoothened-mediated pigment aggregation was reversed by treatment with pertussis toxin or by co-expression with dominant neg. G.alpha.i. The ability of melanophores to express functional Smoothened was also detd. by its co-expression with

the 12-pass transmembrane protein, Patched. Patched blocked Smoothened-mediated melanosome aggregation in a dose-dependent manner, consistent with its physiol. role as an **inhibitor** of Smoothened. That the reconstituted Patched-Smoothened receptor complex functions **normally** in pigment cells was demonstrated by co-transfection with the activating ligand, Sonic **hedgehog**, as well as by direct application of the recombinant Sonic **hedgehog** protein. Sonic **hedgehog** reversed Patched-mediated **inhibition** of Smoothened and induced pigment aggregation. The findings demonstrate that the human Sonic **hedgehog** receptor complex can be functionally reconstituted in melanophores and that it is capable of transmembrane signaling by utilizing endogenous G.alpha.i.

RE.CNT 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

AB The 7-pass transmembrane protein Smoothened was investigated for its ability to act as a G-protein-coupled receptor in Xenopus laevis melanophores. A plasmid contg. the human Smoothened cDNA insert was transfected into immortalized frog pigment cells. Cells expressing the protein showed a phenotype of persistent pigment aggregation, a hallmark of constitutive G.alpha.i activation. Smoothened-mediated pigment aggregation was reversed by treatment with pertussis toxin or by co-expression with dominant neg. G.alpha.i. The ability of melanophores to express functional Smoothened was also detd. by its co-expression with the 12-pass transmembrane protein, Patched. Patched blocked Smoothened-mediated melanosome aggregation in a dose-dependent manner, consistent with its physiol. role as an **inhibitor** of Smoothened. That the reconstituted Patched-Smoothened receptor complex functions **normally** in pigment cells was demonstrated by co-transfection with the activating ligand, Sonic **hedgehog**, as well as by direct application of the recombinant Sonic **hedgehog** protein. Sonic **hedgehog** reversed Patched-mediated **inhibition** of Smoothened and induced pigment aggregation. The findings demonstrate that the human Sonic **hedgehog** receptor complex can be functionally reconstituted in melanophores and that it is capable of transmembrane signaling by utilizing endogenous G.alpha.i.

L4 ANSWER 43 OF 75 CAPLUS COPYRIGHT 2003 ACS on STN
AN 2000:493313 CAPLUS
DN 133:99549
TI Regulation of the hedgehog pathway and smoothened gain-of-function by gene patched agonists
IN Dudek, Henryk; Ji, Benxiu
PA Ontogeny, Inc., USA
SO PCT Int. Appl., 114 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2000041545	A2	20000720	WO 2000-US873	20000113
	WO 2000041545	A3	20000928		

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE,

DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

	US 6291516	B1	20010918	US 1999-417564	19991014
	EP 1143961	A2	20011017	EP 2000-906910	20000113
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
	JP 2003517279	T2	20030527	JP 2000-593166	20000113
	US 2001034337	A1	20011025	US 2001-867311	20010529
PRAI	US 1999-115642P	P	19990113		
	US 1999-119594P	P	19990210		
	US 1999-142124P	P	19990702		
	US 1999-417564	A	19991014		
	WO 2000-US873	W	20000113		

OS MARPAT 133:99549

AB The present invention makes available methods and reagents for **inhibiting** aberrant growth states resulting from **hedgehog** gain-of-function, patched (ptc) loss-of-function or smoothened gain-of-function comprising contacting a cell with a compd., such as a polypeptide or small mol. in an amt. sufficient to control the aberrant growth state, e.g., to agonize a **normal** ptc pathway or antagonize smoothened or **hedgehog** activity. The present invention further makes available methods and reagents for ameliorating the consequences of **hedgehog** loss-of-function, ptc gain-of-function, or smoothened loss-of-function comprising contacting a cell with a compd., such as a polypeptide or small mol., in an amt. sufficient for amelioration. In certain embodiments, the subject compds., e.g., a cAMP analog, adenylate cyclase agonist, or cAMP phosphodiesterase **inhibitor**, regulate cAMP levels, which in turn modulates activity of the **hedgehog** pathway. Thus, compds. such as jervine, cyclopamine, and forskolin analogs are also effective in **inhibition** of medulloblastoma.

AB The present invention makes available methods and reagents for **inhibiting** aberrant growth states resulting from **hedgehog** gain-of-function, patched (ptc) loss-of-function or smoothened gain-of-function comprising contacting a cell with a compd., such as a polypeptide or small mol. in an amt. sufficient to control the aberrant growth state, e.g., to agonize a **normal** ptc pathway or antagonize smoothened or **hedgehog** activity. The present invention further makes available methods and reagents for ameliorating the consequences of **hedgehog** loss-of-function, ptc gain-of-function, or smoothened loss-of-function comprising contacting a cell with a compd., such as a polypeptide or small mol., in an amt. sufficient for amelioration. In certain embodiments, the subject compds., e.g., a cAMP analog, adenylate cyclase agonist, or cAMP phosphodiesterase **inhibitor**, regulate cAMP levels, which in turn modulates activity of the **hedgehog** pathway. Thus, compds. such as jervine, cyclopamine, and forskolin analogs are also effective in **inhibition** of medulloblastoma.

L4 ANSWER 44 OF 75 CAPLUS COPYRIGHT 2003 ACS on STN

AN 2000:446182 CAPLUS

DN 133:162049

TI Inhibition of sonic hedgehog autoprocessing in cultured mammalian cells by sterol deprivation

AU Guy, R. Kip

CS Department of Molecular Genetics, Southwestern Medical Center, University of Texas, Dallas, TX, 75235, USA

SO Proceedings of the National Academy of Sciences of the United States of America (2000), 97(13), 7307-7312

CODEN: PNASA6; ISSN: 0027-8424
PB National Academy of Sciences
DT Journal
LA English
AB Sonic **hedgehog** (Shh) is a signaling mol. that is important for defining patterning in the developing vertebrate central nervous system. After translation, Shh autoproteolyzes and covalently attaches cholesterol to the newly formed carboxyl terminus, a modification crucial for **normal** Shh signaling. Presented here is evidence that acute severe sterol deprivation in cultured Chinese hamster ovary cells expressing mouse Shh (mShh) **inhibits** autoprocessing of the protein. These conditions allowed the first detailed kinetic anal. of mShh autoprocessing and turnover rates revealing that cells rapidly degrade both precursor and mature mShh regardless of sterol content and sterol deprivation increases the rate of precursor degrdn. **Inhibition** of mShh autoprocessing also allowed the detn. of the subcellular localization of mShh precursor which accumulates in a pre-medial Golgi intracellular compartment. Finally, the precursor form of mShh that results from autoprocessing **inhibition** appears to accumulate as an amide rather than a stable thioester.
RE.CNT 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT
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L4 ANSWER 45 OF 75 CAPLUS COPYRIGHT 2003 ACS on STN
AN 2000:223004 CAPLUS
DN 132:319917
TI Control of chick tectum territory along dorsoventral axis by Sonic hedgehog
AU Watanabe, Yuji; Nakamura, Harukazu
CS Department of Molecular Neurobiology, Institute of Development, Aging and Cancer, Tohoku University, Sendai, 980-8575, Japan
SO Development (Cambridge, United Kingdom) (2000), 127(5), 1131-1140
CODEN: DEVPED; ISSN: 0950-1991
PB Company of Biologists Ltd.
DT Journal
LA English
AB Chick midbrain comprises 2 major components along the dorsoventral axis, the tectum and the tegmentum. The alar plate differentiates into the optic tectum, while the basal plate gives rise to the tegmentum. It is largely unknown how the differences between these 2 structures are molecularly controlled during the midbrain development. The secreted protein Sonic **hedgehog** (Shh) produced in the notochord and floor plate induces differentiation of ventral cell types of the central nervous

system. To evaluate the role of Shh in the establishment of dorsoventral polarity in the developing midbrain, we have ectopically expressed Shh unilaterally in the brain vesicles including whole midbrain of E1.5 chick embryos in ovo. Ectopic Shh repressed **normal** growth of the tectum, producing dorsally enlarged tegmentum region. In addn., the expression of several genes crucial for tectum formation was strongly suppressed in the midbrain and isthmus. Markers for midbrain roof plate were **inhibited**, indicating that the roof plate was not fully generated. After E5, the tectum territory of Shh-transfected side was significantly reduced and was fused with that of untransfected side. Moreover, ectopic Shh induced a considerable no. of SC1-pos. motor neurons, overlapping markers such as HNF-3.beta. (floor plate), Isl-1 (postmitotic motor neuron) and Lim1/2. Dopaminergic and serotonergic neurons were also generated in the dorsally extended region. These changes indicate that ectopic Shh changed the fate of the mesencephalic alar plate to that of the basal plate, suppressing the massive cell proliferation that **normally** occurs in the developing tectum. Taken together our results suggest that Shh signaling restricts the tectum territory by controlling the mol. cascade for tectum formation along dorsoventral axis and by regulating neuronal cell diversity in the ventral midbrain.

RE.CNT 64 THERE ARE 64 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

AB Chick midbrain comprises 2 major components along the dorsoventral axis, the tectum and the tegmentum. The alar plate differentiates into the optic tectum, while the basal plate gives rise to the tegmentum. It is largely unknown how the differences between these 2 structures are molecularly controlled during the midbrain development. The secreted protein Sonic **hedgehog** (Shh) produced in the notochord and floor plate induces differentiation of ventral cell types of the central nervous system. To evaluate the role of Shh in the establishment of dorsoventral polarity in the developing midbrain, we have ectopically expressed Shh unilaterally in the brain vesicles including whole midbrain of E1.5 chick embryos in ovo. Ectopic Shh repressed **normal** growth of the tectum, producing dorsally enlarged tegmentum region. In addn., the expression of several genes crucial for tectum formation was strongly suppressed in the midbrain and isthmus. Markers for midbrain roof plate were **inhibited**, indicating that the roof plate was not fully generated. After E5, the tectum territory of Shh-transfected side was significantly reduced and was fused with that of untransfected side. Moreover, ectopic Shh induced a considerable no. of SC1-pos. motor neurons, overlapping markers such as HNF-3.beta. (floor plate), Isl-1 (postmitotic motor neuron) and Lim1/2. Dopaminergic and serotonergic neurons were also generated in the dorsally extended region. These changes indicate that ectopic Shh changed the fate of the mesencephalic alar plate to that of the basal plate, suppressing the massive cell proliferation that **normally** occurs in the developing tectum. Taken together our results suggest that Shh signaling restricts the tectum territory by controlling the mol. cascade for tectum formation along dorsoventral axis and by regulating neuronal cell diversity in the ventral midbrain.

L4 ANSWER 46 OF 75 CAPLUS COPYRIGHT 2003 ACS on STN
AN 1999:721191 CAPLUS
DN 132:47933
TI Proteolysis of cubitus interruptus in Drosophila requires phosphorylation by protein kinase A
AU Price, Mary Ann; Kalderon, Daniel
CS Department of Biological Sciences, Columbia University, New York, NY,

10027, USA
SO Development (Cambridge, United Kingdom) (1999), 126(19), 4331-4339
CODEN: DEVPED; ISSN: 0950-1991
PB Company of Biologists Ltd.
DT Journal
LA English
AB In Drosophila, **Hedgehog** signaling regulates transcription of target genes by modifying the activity of the DNA-binding protein Cubitus interruptus (Ci). **Hedgehog** signaling **inhibits** proteolytic cleavage of full-length Ci (Ci-155) to Ci-75, a form that represses some target genes, and also converts the full-length form to a potent transcriptional activator. Redn. of protein kinase A (PKA) activity also leads to accumulation of full-length Ci and to ectopic expression of **Hedgehog** target genes, prompting the hypothesis that PKA might **normally** promote cleavage to Ci-75 by directly phosphorylating Ci-155. Here we show that a mutant form of Ci lacking 5 potential PKA phosphorylation sites (Ci5m) is not detectably cleaved to Ci-75 in Drosophila embryos. Moreover, changes in PKA activity dramatically altered levels of full-length wild-type Ci in embryos and imaginal disks, but did not significantly alter full-length Ci5m levels. We corroborate these results by showing that Ci5m is more active than wild-type Ci at inducing ectopic transcription of the Hh target gene wingless in embryos and that **inhibition** of PKA enhances induction of wingless by wild-type Ci but not by Ci5m. We therefore propose that PKA phosphorylation of Ci is required for the proteolysis of Ci-155 to Ci-75 in vivo. We also show that the activity of Ci5m remains **Hedgehog** responsive if expressed at low levels, providing further evidence that the full-length form of Ci undergoes a **Hedgehog** -dependent activation step.
RE.CNT 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT
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L4 ANSWER 47 OF 75 CAPLUS COPYRIGHT 2003 ACS on STN
AN 1999:523933 CAPLUS
DN 131:267798
TI Gli proteins encode context-dependent positive and negative functions:

implications for development and disease
AU Ruiz i Altaba, A.
CS The Skirball Institute, Developmental Genetics Program and Department of Cell Biology, NYU School of Medicine, New York, NY, 10016, USA
SO Development (Cambridge, United Kingdom) (1999), 126(14), 3205-3216
CODEN: DEVPED; ISSN: 0950-1991
PB Company of Biologists Ltd.
DT Journal
LA English
AB Several lines of evidence implicate zinc finger proteins of the Gli family in the final steps of **Hedgehog** signaling in **normal** development and disease. C-terminally truncated mutant GLI3 proteins are also assocd. with human syndromes, but it is not clear whether these C-terminally truncated Gli proteins fulfil the same function as full-length ones. Here, structure-function analyses of Gli proteins have been performed using floor plate and neuronal induction assays in frog embryos, as well as induction of alk. phosphatase (AP) in SHH-responsive mouse C3H10T1/2 cells. These assays show that C-terminal sequences are required for pos. inducing activity and cytoplasmic localization, whereas N-terminal sequences det. dominant neg. function and nuclear localization. Analyses of nuclear targeted Gli1 and Gli2 proteins suggest that both activator and dominant neg. proteins are modified forms. In embryos and COS cells, tagged Gli cDNAs yield C-terminally deleted forms similar to that of Ci. These results thus provide a mol. basis for the human Polydactyly type A and Pallister-Hall Syndrome phenotypes, derived from the deregulated prodn. of C-terminally truncated GLI3 proteins. Analyses of full-length Gli function in 10T1/2 cells suggest that nuclear localization of activating forms is a regulated event and show that only Gli1 mimics SHH in inducing AP activity. Moreover, full-length Gli3 and all C-terminally truncated forms act antagonistically whereas Gli2 is inactive in this assay. In 10T1/2 cells, protein kinase A (PKA), a known **inhibitor** of Hh signaling, promotes Gli3 repressor formation and **inhibits** Gli1 function. Together, these findings suggest a context-dependent functional divergence of Gli protein function, in which a cell represses Gli3 and activates Gli1/2 prevents the formation of repressor Gli forms to respond to Shh. Interpretation of Hh signals by Gli proteins therefore appears to involve a fine balance of divergent functions within each and among different Gli proteins, the misregulation of which has profound biol. consequences.
RE.CNT 60 THERE ARE 60 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT
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localization of activating forms is a regulated event and show that only Gli1 mimics SHH in inducing AP activity. Moreover, full-length Gli3 and all C-terminally truncated forms act antagonistically whereas Gli2 is inactive in this assay. In 10T1/2 cells, protein kinase A (PKA), a known **inhibitor** of Hh signaling, promotes Gli3 repressor formation and **inhibits** Gli1 function. Together, these findings suggest a context-dependent functional divergence of Gli protein function, in which a cell represses Gli3 and activates Gli1/2 prevents the formation of repressor Gli forms to respond to Shh. Interpretation of Hh signals by Gli proteins therefore appears to involve a fine balance of divergent functions within each and among different Gli proteins, the misregulation of which has profound biol. consequences.

L4 ANSWER 48 OF 75 CAPLUS COPYRIGHT 2003 ACS on STN
AN 1999:461941 CAPLUS
DN 131:182549
TI Wnt-7a in feather morphogenesis: involvement of anterior-posterior asymmetry and proximal-distal elongation demonstrated with an in vitro reconstitution model
AU Widelitz, Randall B.; Jiang, Ting-Xin; Chen, Chia-Wei Janet; Stott, N. Susan; Chuong, Cheng-Ming
CS Department of Pathology, School of Medicine, University of Southern California, Los Angeles, CA, 90033, USA
SO Development (Cambridge, United Kingdom) (1999), 126(12), 2577-2587
CODEN: DEVPED; ISSN: 0950-1991
PB Company of Biologists Ltd.
DT Journal
LA English
AB How do vertebrate epithelial appendages form from the flat epithelia. Following the formation of feather placodes, the previously radially sym. primordia become anterior-posterior (A-P) asym. and develop a proximo-distal (P-D) axis. Anal. of the mol. heterogeneity revealed a surprising parallel of mol. profiles in the A-P feather buds and the ventral-dorsal (V-D) Drosophila appendage imaginal disks. The functional significance was tested with an in vitro feather reconstitution model. Wnt-7a expression initiated all over the feather tract epithelium, intensifying as it became restricted first to the primordia domain, then to an accentuated ring pattern within the primordia border, and finally to the posterior bud. In contrast, sonic **hedgehog** expression was induced later as a dot within the primordia. RCAS was used to overexpress Wnt-7a in reconstituted feather explants derived from stage 29 dorsal skin to further test its function in feather formation. Control skin formed **normal** elongated, slender buds with A-P orientation, but Wnt-7a overexpression led to plateau-like skin appendages lacking an A-P axis. Feathers in the Wnt-7a overexpressing skin also had **inhibited** elongation of the P-D axes. This was not due to a lack of cell proliferation, which actually was increased although randomly distributed. While morphogenesis was perturbed, differentiation proceeded as indicated by the formation of barb ridges. Wnt-7a buds have reduced expression of anterior (Tenascin) bud markers. Middle (Notch-1) and posterior bud markers including Delta-1 and Serrate-1 were diffusely expressed. The results showed that ectopic Wnt-7a expression enhanced properties characteristic of the middle and posterior feather buds and suggest that P-D elongation of vertebrate skin appendages requires balanced interactions between the anterior and posterior buds.
RE.CNT 66 THERE ARE 66 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT
AB How do vertebrate epithelial appendages form from the flat epithelia. Following the formation of feather placodes, the previously radially sym.

primordia become anterior-posterior (A-P) asym. and develop a proximo-distal (P-D) axis. Anal. of the mol. heterogeneity revealed a surprising parallel of mol. profiles in the A-P feather buds and the ventral-dorsal (V-D) Drosophila appendage imaginal disks. The functional significance was tested with an in vitro feather reconstitution model. Wnt-7a expression initiated all over the feather tract epithelium, intensifying as it became restricted first to the primordia domain, then to an accentuated ring pattern within the primordia border, and finally to the posterior bud. In contrast, sonic **hedgehog** expression was induced later as a dot within the primordia. RCAS was used to overexpress Wnt-7a in reconstituted feather explants derived from stage 29 dorsal skin to further test its function in feather formation. Control skin formed **normal** elongated, slender buds with A-P orientation, but Wnt-7a overexpression led to plateau-like skin appendages lacking an A-P axis. Feathers in the Wnt-7a overexpressing skin also had **inhibited** elongation of the P-D axes. This was not due to a lack of cell proliferation, which actually was increased although randomly distributed. While morphogenesis was perturbed, differentiation proceeded as indicated by the formation of barb ridges. Wnt-7a buds have reduced expression of anterior (Tenascin) bud markers. Middle (Notch-1) and posterior bud markers including Delta-1 and Serrate-1 were diffusely expressed. The results showed that ectopic Wnt-7a expression enhanced properties characteristic of the middle and posterior feather buds and suggest that P-D elongation of vertebrate skin appendages requires balanced interactions between the anterior and posterior buds.

L4 ANSWER 49 OF 75 CAPLUS COPYRIGHT 2003 ACS on STN
AN 1999:425285 CAPLUS
DN 131:240861
TI Overexpression of ptc1 Inhibits Induction of Shh Target Genes and Prevents Normal Patterning in the Neural Tube
AU Goodrich, Lisa V.; Jung, David; Higgins, Kay M.; Scott, Matthew P.
CS Department of Developmental Biology, Stanford University School of Medicine, Stanford, CA, 94305-5427, USA
SO Developmental Biology (1999), 211(2), 323-334
CODEN: DEBIAO; ISSN: 0012-1606
PB Academic Press
DT Journal
LA English
AB Patched (Ptc) is a human tumor suppressor protein and a candidate receptor for **Hedgehog** (Hh) proteins, which regulate growth and patterning in embryos. Ptc represses expression of Hh target genes such as Gli1 and ptc1 itself. Localized secretion of Hh appears to induce transcription of target genes in specific patterns by binding to Ptc and preventing it from functioning in recipient cells. People who are heterozygous for PTC1 exhibit a range of developmental defects, suggesting that some genes are inappropriately expressed when there is not enough Ptc protein. To test the idea that a balance between Hh and Ptc activities is essential for **normal** development, we overexpressed Ptc in the neural tube. We find that excess Ptc is sufficient to **inhibit** expression of Gli1 and ptc1, suggesting that Sonic **hedgehog** (Shh) cannot signal effectively. This leads to partial dorsalization of the neural tube and a wide spectrum of neural defects, ranging from embryonic lethality to hydrocephaly. (c) 1999 Academic Press.
RE.CNT 77 THERE ARE 77 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT
AB Patched (Ptc) is a human tumor suppressor protein and a candidate receptor for **Hedgehog** (Hh) proteins, which regulate growth and patterning in embryos. Ptc represses expression of Hh target genes such as Gli1 and

ptc1 itself. Localized secretion of Hh appears to induce transcription of target genes in specific patterns by binding to Ptc and preventing it from functioning in recipient cells. People who are heterozygous for PTC1 exhibit a range of developmental defects, suggesting that some genes are inappropriately expressed when there is not enough Ptc protein. To test the idea that a balance between Hh and Ptc activities is essential for **normal** development, we overexpressed Ptc in the neural tube. We find that excess Ptc is sufficient to **inhibit** expression of Gli1 and ptc1, suggesting that Sonic **hedgehog** (Shh) cannot signal effectively. This leads to partial dorsalization of the neural tube and a wide spectrum of neural defects, ranging from embryonic lethality to hydrocephaly. (c) 1999 Academic Press.

IT **Hedgehog** protein
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(sonic; overexpression of ptc1 **inhibits** induction of Shh target genes and prevents **normal** patterning in the neural tube)

L4 ANSWER 50 OF 75 CAPLUS COPYRIGHT 2003 ACS on STN
AN 1999:411874 CAPLUS
DN 131:182572
TI Sonic hedgehog signaling is required during the appearance of spinal cord oligodendrocyte precursors
AU Orentas, Diana M.; Hayes, Jeannette E.; Dyer, Kimberly L.; Miller, Robert H.
CS Department of Neurosciences, Case Western Reserve University, Cleveland, OH, 44106, USA
SO Development (Cambridge, United Kingdom) (1999), 126(11), 2419-2429
CODEN: DEVPED; ISSN: 0950-1991
PB Company of Biologists Ltd.
DT Journal
LA English
AB Spinal cord oligodendrocyte precursors arise in the ventral ventricular zone as a result of local signals. Ectopic oligodendrocyte precursors can be induced by sonic **hedgehog** (Shh) in explants of chick dorsal spinal cord over an extended developmental period. The role of Shh during **normal** oligodendrocyte development is, however, unclear. Here we demonstrate that Shh is localized to the ventral spinal cord immediately prior to, and during the appearance of oligodendrocyte precursors. Continued expression of Shh is required for the appearance of spinal cord oligodendrocyte precursors as neutralization of Shh signaling both in vivo and in vitro during a defined developmental period blocked their emergence. The **inhibition** of oligodendrocyte precursor emergence in the absence of Shh signaling was not the result of **inhibiting** precursor cell proliferation, and the neutralization of Shh signaling after the emergence of oligodendrocyte precursors had no effect on the appearance of addnl. cells or their subsequent differentiation. Similar concns. of Shh induce motor neurons and oligodendrocytes in dorsal spinal cord explants. However, in explants from early embryos the motor neuron lineage is preferentially expanded while in explants from older embryos the oligodendrocyte lineage is preferentially expanded.
RE.CNT 57 THERE ARE 57 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT
AB Spinal cord oligodendrocyte precursors arise in the ventral ventricular zone as a result of local signals. Ectopic oligodendrocyte precursors can be induced by sonic **hedgehog** (Shh) in explants of chick dorsal spinal cord over an extended developmental period. The role of Shh during

normal oligodendrocyte development is, however, unclear. Here we demonstrate that Shh is localized to the ventral spinal cord immediately prior to, and during the appearance of oligodendrocyte precursors. Continued expression of Shh is required for the appearance of spinal cord oligodendrocyte precursors as neutralization of Shh signaling both in vivo and in vitro during a defined developmental period blocked their emergence. The **inhibition** of oligodendrocyte precursor emergence in the absence of Shh signaling was not the result of **inhibiting** precursor cell proliferation, and the neutralization of Shh signaling after the emergence of oligodendrocyte precursors had no effect on the appearance of addnl. cells or their subsequent differentiation. Similar concns. of Shh induce motor neurons and oligodendrocytes in dorsal spinal cord explants. However, in explants from early embryos the motor neuron lineage is preferentially expanded while in explants from older embryos the oligodendrocyte lineage is preferentially expanded.

L4 ANSWER 51 OF 75 CAPLUS COPYRIGHT 2003 ACS on STN
AN 1999:241724 CAPLUS
DN 131:42339
TI The function of cholesterol in embryogenesis
AU Wolf, George
CS Department of Nutritional Sciences, University of California, Berkeley, CA, 94720, USA
SO Journal of Nutritional Biochemistry (1999), 10(4), 188-192
CODEN: JNBIEL; ISSN: 0955-2863
PB Elsevier Science Inc.
DT Journal; General Review
LA English
AB A review with 38 refs. Cholesterol is crit. in embryonic development. **Inhibition** of cholesterol synthesis in exptl. animals has caused a birth defect called holoprosencephaly (HPE), which is evidenced by cyclopia (one eye in the middle of the face), monorhinia (protruding single nose above the eye), absence of the pituitary gland, and central nervous system (CNS) abnormalities. In humans, an inherited defect in the cholesterol-synthesizing enzyme 7-dehydrocholesterol reductase depletes cholesterol and results in human HPE, termed Smith-Lemli-Opitz syndrome. In its most severe form, the syndrome leads to cyclopia, monorhinia, and lack of sepn. of cerebral hemispheres. The cause of the syndrome is a defect in a protein coded by the gene Sonic **hedgehog** (SHH). The protein SHH is expressed in the notochord of the CNS in the early embryo and is activated by being cleaved autocatalytically, with simultaneous covalent attachment of cholesterol to the N-terminal fragment, which is secreted by cells of the mesoderm layer, signaling the establishment of the neural midline cells. Thus, cholesterol is essential for proper signaling in the development of the **normal** embryo.
RE.CNT 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT
AB A review with 38 refs. Cholesterol is crit. in embryonic development. **Inhibition** of cholesterol synthesis in exptl. animals has caused a birth defect called holoprosencephaly (HPE), which is evidenced by cyclopia (one eye in the middle of the face), monorhinia (protruding single nose above the eye), absence of the pituitary gland, and central nervous system (CNS) abnormalities. In humans, an inherited defect in the cholesterol-synthesizing enzyme 7-dehydrocholesterol reductase depletes cholesterol and results in human HPE, termed Smith-Lemli-Opitz syndrome. In its most severe form, the syndrome leads to cyclopia, monorhinia, and lack of sepn. of cerebral hemispheres. The cause of the syndrome is a defect in a protein coded by the gene Sonic **hedgehog** (SHH). The

protein SHH is expressed in the notochord of the CNS in the early embryo and is activated by being cleaved autocatalytically, with simultaneous covalent attachment of cholesterol to the N-terminal fragment, which is secreted by cells of the mesoderm layer, signaling the establishment of the neural midline cells. Thus, cholesterol is essential for proper signaling in the development of the **normal** embryo.

L4 ANSWER 52 OF 75 CAPLUS COPYRIGHT 2003 ACS on STN
AN 1999:219007 CAPLUS
DN 130:349925
TI BMPs negatively regulate structure and function of the limb apical ectodermal ridge
AU Pizette, Sandrine; Niswander, Lee
CS Molecular Biology Program, Memorial Sloan-Kettering Cancer Center, New York, NY, 10021, USA
SO Development (Cambridge, United Kingdom) (1999), 126(5), 883-894
CODEN: DEVPED; ISSN: 0950-1991
PB Company of Biologists Ltd.
DT Journal
LA English
AB The apical ectodermal ridge (AER), a transient specialized epithelium at the distal limb tip, is essential for vertebrate embryonic limb outgrowth along the proximodistal axis. Among all the mols. expressed in the AER, only the FGFs have been shown to substitute for its function in limb outgrowth. After specification of the skeletal progenitors is complete, the AER regresses, having fulfilled its function. However, the cellular processes underlying AER regression remain largely unclear, and the mol. ones, totally unknown. Members of the Bone Morphogenetic Protein (BMP) family are expressed in the AER throughout its life and in the mesenchyme. Our studies using misexpression of Noggin, a BMP **inhibitor**, reveal an unsuspected role for BMPs in the neg. regulation of FGF expression and AER function. We find that BMPs limit limb outgrowth by promoting AER regression, as BMP **inhibition** results in persistence of the AER, prolonged FGF expression and excess soft-tissue growth. In addn., the Noggin misexpression studies uncover an earlier role for BMPs in repression of AER function. Noggin overexpression results in extension of the AER anteriorly and loss of AER asymmetry. We show that overall the AER becomes taller, and its anterior half becomes more similar to a **normal** posterior AER. In addn., FGF4 transcripts, which are usually restricted to the posterior half of the AER, are now also expressed anteriorly. Moreover, ectopic FGF4 expression is induced independently of Sonic **Hedgehog**, contrary to current models of FGF4 regulation in the limb. Our studies also provide insight into the activity of the hypothesized apical ectodermal maintenance factor (AEMF), which is thought to maintain the tall shape of the posterior part of the AER. Our work shows that the AER is neg. regulated by BMP.
RE.CNT 64 THERE ARE 64 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT
AB The apical ectodermal ridge (AER), a transient specialized epithelium at the distal limb tip, is essential for vertebrate embryonic limb outgrowth along the proximodistal axis. Among all the mols. expressed in the AER, only the FGFs have been shown to substitute for its function in limb outgrowth. After specification of the skeletal progenitors is complete, the AER regresses, having fulfilled its function. However, the cellular processes underlying AER regression remain largely unclear, and the mol. ones, totally unknown. Members of the Bone Morphogenetic Protein (BMP) family are expressed in the AER throughout its life and in the mesenchyme. Our studies using misexpression of Noggin, a BMP **inhibitor**, reveal an unsuspected role for BMPs in the neg. regulation of FGF

expression and AER function. We find that BMPs limit limb outgrowth by promoting AER regression, as BMP **inhibition** results in persistence of the AER, prolonged FGF expression and excess soft-tissue growth. In addn., the Noggin misexpression studies uncover an earlier role for BMPs in repression of AER function. Noggin overexpression results in extension of the AER anteriorly and loss of AER asymmetry. We show that overall the AER becomes taller, and its anterior half becomes more similar to a **normal** posterior AER. In addn., FGF4 transcripts, which are usually restricted to the posterior half of the AER, are now also expressed anteriorly. Moreover, ectopic FGF4 expression is induced independently of Sonic **Hedgehog**, contrary to current models of FGF4 regulation in the limb. Our studies also provide insight into the activity of the hypothesized apical ectodermal maintenance factor (AEMF), which is thought to maintain the tall shape of the posterior part of the AER. Our work shows that the AER is neg. regulated by BMP.

L4 ANSWER 53 OF 75 CAPLUS COPYRIGHT 2003 ACS on STN
AN 1999:105197 CAPLUS
DN 130:265440
TI Control of neuronal precursor proliferation in the cerebellum by sonic hedgehog
AU Wechsler-Reya, Robert J.; Scott, Matthew P.
CS Departments of Developmental Biology and Genetics Howard Hughes Medical Institute, Stanford University School of Medicine, Stanford, CA, 94305, USA
SO Neuron (1999), 22(1), 103-114
CODEN: NERNET; ISSN: 0896-6273
PB Cell Press
DT Journal
LA English
AB Cerebellar granule cells are the most abundant type of neuron in the brain, but the mol. mechanisms that control their generation are incompletely understood. We show that Sonic **hedgehog** (Shh), which is made by Purkinje cells, regulates the division of granule cell precursors (GCPs). Treatment of GCPs with Shh prevents differentiation and induces a potent, long-lasting proliferative response. This response can be **inhibited** by basic fibroblast growth factor or by activation of protein kinase A. Blocking Shh function in vivo dramatically reduces GCP proliferation. These findings provide insight into the mechanisms of **normal** growth and tumorigenesis in the cerebellum.
RE.CNT 82 THERE ARE 82 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT
AB Cerebellar granule cells are the most abundant type of neuron in the brain, but the mol. mechanisms that control their generation are incompletely understood. We show that Sonic **hedgehog** (Shh), which is made by Purkinje cells, regulates the division of granule cell precursors (GCPs). Treatment of GCPs with Shh prevents differentiation and induces a potent, long-lasting proliferative response. This response can be **inhibited** by basic fibroblast growth factor or by activation of protein kinase A. Blocking Shh function in vivo dramatically reduces GCP proliferation. These findings provide insight into the mechanisms of **normal** growth and tumorigenesis in the cerebellum.

L4 ANSWER 54 OF 75 CAPLUS COPYRIGHT 2003 ACS on STN
AN 1999:94481 CAPLUS
DN 130:265307
TI Mice lacking link protein develop dwarfism and craniofacial abnormalities

AU Watanabe, Hideto; Yamada, Yoshihiko
CS Craniofacial Developmental Biology and Regeneration Branch, National Institute of Dental and Craniofacial Research, National Institutes of Health, Bethesda, MD, 20892, USA
SO Nature Genetics (1999), 21(2), 225-229
CODEN: NGENEC; ISSN: 1061-4036
PB Nature America
DT Journal
LA English
AB Link protein (LP), an extracellular matrix protein in cartilage, stabilizes aggregates of aggrecan and hyaluronan, giving cartilage its tensile strength and elasticity. Cartilage provides the template for endochondral ossification and is crucial for detg. the length and width of the skeleton. During endochondral bone formation, hypertrophic chondrocytes die and the cartilage is replaced with bone matrix. Here, we have generated targeted mutations in mice in the gene encoding LP (Crtl1). Homozygotes showed defects in cartilage development and delayed bone formation with short limbs and craniofacial anomalies. Most Crtl1tm1Nid/tm1Nid mice died shortly after birth due to respiratory failure, but some survived and developed progressive dwarfism and lordosis of the cervical spine. They showed small epiphysis, slightly flared metaphysis of long bones and flattened vertebrae, characteristic of spondyloepiphyseal dysplasias. The cartilage contained significantly reduced aggrecan depositions in the hypertrophic zone, and decreased nos. of prehypertrophic and hypertrophic chondrocytes. Reduced Indian **hedgehog** (Ihh) expression was obsd. in prehypertrophic chondrocytes, and apoptosis was **inhibited** in hypertrophic chondrocytes. These results indicate that LP is important for the formation of proteoglycan aggregates and **normal** organization of hypertrophic chondrocytes, and suggest that cartilage matrix has a role in chondrocyte differentiation and maturation.
RE.CNT 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT
AB Link protein (LP), an extracellular matrix protein in cartilage, stabilizes aggregates of aggrecan and hyaluronan, giving cartilage its tensile strength and elasticity. Cartilage provides the template for endochondral ossification and is crucial for detg. the length and width of the skeleton. During endochondral bone formation, hypertrophic chondrocytes die and the cartilage is replaced with bone matrix. Here, we have generated targeted mutations in mice in the gene encoding LP (Crtl1). Homozygotes showed defects in cartilage development and delayed bone formation with short limbs and craniofacial anomalies. Most Crtl1tm1Nid/tm1Nid mice died shortly after birth due to respiratory failure, but some survived and developed progressive dwarfism and lordosis of the cervical spine. They showed small epiphysis, slightly flared metaphysis of long bones and flattened vertebrae, characteristic of spondyloepiphyseal dysplasias. The cartilage contained significantly reduced aggrecan depositions in the hypertrophic zone, and decreased nos. of prehypertrophic and hypertrophic chondrocytes. Reduced Indian **hedgehog** (Ihh) expression was obsd. in prehypertrophic chondrocytes, and apoptosis was **inhibited** in hypertrophic chondrocytes. These results indicate that LP is important for the formation of proteoglycan aggregates and **normal** organization of hypertrophic chondrocytes, and suggest that cartilage matrix has a role in chondrocyte differentiation and maturation.

L4 ANSWER 55 OF 75 CAPLUS COPYRIGHT 2003 ACS on STN
AN 1999:67403 CAPLUS
DN 130:235209

TI Essential role for Sonic hedgehog during hair follicle morphogenesis
AU Chiang, Chin; Swan, Ryan Z.; Grachtchouk, Marina; Bolinger, Matthew; Litingtung, Ying; Robertson, Erin K.; Cooper, Michael K.; Gaffield, William; Westphal, Heiner; Beachy, Philip A.; Dlugosz, Andrzej A.
CS Laboratory of Mammalian Genes and Development, National Institutes of Health, Bethesda, MD, 20892, USA
SO Developmental Biology (1999), 205(1), 1-9
CODEN: DEBIAO; ISSN: 0012-1606
PB Academic Press
DT Journal
LA English
AB The hair follicle is a source of epithelial stem cells and site of origin for several types of skin tumors. Although it is clear that follicles arise by way of a series of inductive tissue interactions, identification of the signaling mols. driving this process remains a major challenge in skin biol. In this study we report an obligatory role for the secreted morphogen Sonic **hedgehog** (Shh) during hair follicle development. Hair germs comprising epidermal placodes and assocd. dermal condensates were detected in both control and Shh -/- embryos, but progression through subsequent stages of follicle development was blocked in mutant skin. The expression of Gli1 and Ptc1 was reduced in Shh -/- dermal condensates and they failed to evolve into hair follicle papillae, suggesting that the adjacent mesenchyme is a crit. target for placode-derived Shh. Despite the profound **inhibition** of hair follicle morphogenesis, late-stage follicle differentiation markers were detected in Shh -/- skin grafts, as well as cultured vibrissa explants treated with cyclopamine to block Shh signaling. Our findings reveal an essential role for Shh during hair follicle morphogenesis, where it is required for **normal** advancement beyond the hair germ stage of development. (c) 1999 Academic Press.
RE.CNT 50 THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT
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L4 ANSWER 56 OF 75 CAPLUS COPYRIGHT 2003 ACS on STN
AN 1998:745349 CAPLUS
DN 130:93139
TI Characterization of two patched receptors for the vertebrate hedgehog protein family
AU Carpenter, David; Stone, Donna M.; Brush, Jennifer; Ryan, Anne; Armanini, Mark; Frantz, Gretchen; Rosenthal, Arnon; De Sauvage, Frederic J.

CS Departments of Mol. Oncol., Genentech Inc., South San Francisco, CA, 94080, USA
SO Proceedings of the National Academy of Sciences of the United States of America (1998), 95(23), 13630-13634
CODEN: PNASA6; ISSN: 0027-8424
PB National Academy of Sciences
DT Journal
LA English
AB The multitransmembrane protein Patched (PTCH) is the receptor for Sonic **Hedgehog** (Shh), a secreted mol. implicated in the formation of embryonic structures and in tumorigenesis. Current models suggest that binding of Shh to PTCH prevents the **normal inhibition** of the seven-transmembrane-protein Smoothened (SMO) by PTCH. According to this model, the **inhibition** of SMO signaling is relieved after mutational inactivation of PTCH in the basal cell nevus syndrome. Recently, PTCH2, a mol. with sequence homol. to PTCH, has been identified. To chromatize both PTCH mols. with respect to the various **Hedgehog** proteins, the authors have isolated the human PTCH2 gene. Biochem. anal. of PTCH and PTCH2 shows that they both bind to all **hedgehog** family members with similar affinity and that they can form a complex with SMO. However, the expression patterns of PTCH and PTCH2 do not fully overlap. While PTCH is expressed throughout the mouse embryo, PTCH2 is found at high levels in the skin and in spermatocytes. Because Desert **Hedgehog** (Dhh) is expressed specifically in the testis and is required for germ cell development, it is likely that PTCH2 mediates its activity in vivo. Chromosomal localization of PTCH2 places it on chromosome 1p33-34, a region deleted in some germ cell tumors, raising the possibility that PTCH2 may be a tumor suppressor in Dhh target cells.
RE.CNT 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT
AB The multitransmembrane protein Patched (PTCH) is the receptor for Sonic **Hedgehog** (Shh), a secreted mol. implicated in the formation of embryonic structures and in tumorigenesis. Current models suggest that binding of Shh to PTCH prevents the **normal inhibition** of the seven-transmembrane-protein Smoothened (SMO) by PTCH. According to this model, the **inhibition** of SMO signaling is relieved after mutational inactivation of PTCH in the basal cell nevus syndrome. Recently, PTCH2, a mol. with sequence homol. to PTCH, has been identified. To chromatize both PTCH mols. with respect to the various **Hedgehog** proteins, the authors have isolated the human PTCH2 gene. Biochem. anal. of PTCH and PTCH2 shows that they both bind to all **hedgehog** family members with similar affinity and that they can form a complex with SMO. However, the expression patterns of PTCH and PTCH2 do not fully overlap. While PTCH is expressed throughout the mouse embryo, PTCH2 is found at high levels in the skin and in spermatocytes. Because Desert **Hedgehog** (Dhh) is expressed specifically in the testis and is required for germ cell development, it is likely that PTCH2 mediates its activity in vivo. Chromosomal localization of PTCH2 places it on chromosome 1p33-34, a region deleted in some germ cell tumors, raising the possibility that PTCH2 may be a tumor suppressor in Dhh target cells.

L4 ANSWER 57 OF 75 CAPLUS COPYRIGHT 2003 ACS on STN
AN 1998:676595 CAPLUS
DN 130:35873
TI Decapentaplegic and wingless are regulated by eyes absent and eyegone and interact to direct the pattern of retinal differentiation in the eye disk
AU Hazelett, Dennis J.; Bourouis, Marc; Walldorf, Uwe; Treisman, Jessica E.
CS NYU Medical Center, Skirball Institute for Biomolecular Medicine and Department of Cell Biology, New York, NY, 10016, USA

SO Development (Cambridge, United Kingdom) (1998), 125(18), 3741-3751
CODEN: DEVPED; ISSN: 0950-1991
PB Company of Biologists Ltd.
DT Journal
LA English
AB Signaling by the secreted **hedgehog**, decapentaplegic and wingless proteins organizes the pattern of photoreceptor differentiation within the Drosophila eye imaginal disk; **hedgehog** and decapentaplegic are required for differentiation to initiate at the posterior margin and progress across the disk, while wingless prevents it from initiating at the lateral margins. Our anal. of these interactions has shown that initiation requires both the presence of decapentaplegic and the absence of wingless, which **inhibits** photoreceptor differentiation downstream of the reception of the decapentaplegic signal. However, wingless is unable to **inhibit** differentiation driven by activation of the epidermal growth factor receptor pathway. The effect of wingless is subject to regional variations in control, as the anterior margin of the disk is insensitive to wingless **inhibition**. The eyes absent and eyegone genes encode members of a group of nuclear proteins required to specify the fate of the eye imaginal disk. Both eyes absent and eyegone are required for **normal** activation of decapentaplegic expression at the posterior and lateral margins of the disk, and repression of wingless expression in presumptive retinal tissue. The requirement for eyegone can be alleviated by **inhibition** of the wingless signaling pathway, suggesting that eyegone promotes eye development primarily by repressing wingless. These results provide a link between the early specification and later differentiation of the eye disk.
RE.CNT 103 THERE ARE 103 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT
AB Signaling by the secreted **hedgehog**, decapentaplegic and wingless proteins organizes the pattern of photoreceptor differentiation within the Drosophila eye imaginal disk; **hedgehog** and decapentaplegic are required for differentiation to initiate at the posterior margin and progress across the disk, while wingless prevents it from initiating at the lateral margins. Our anal. of these interactions has shown that initiation requires both the presence of decapentaplegic and the absence of wingless, which **inhibits** photoreceptor differentiation downstream of the reception of the decapentaplegic signal. However, wingless is unable to **inhibit** differentiation driven by activation of the epidermal growth factor receptor pathway. The effect of wingless is subject to regional variations in control, as the anterior margin of the disk is insensitive to wingless **inhibition**. The eyes absent and eyegone genes encode members of a group of nuclear proteins required to specify the fate of the eye imaginal disk. Both eyes absent and eyegone are required for **normal** activation of decapentaplegic expression at the posterior and lateral margins of the disk, and repression of wingless expression in presumptive retinal tissue. The requirement for eyegone can be alleviated by **inhibition** of the wingless signaling pathway, suggesting that eyegone promotes eye development primarily by repressing wingless. These results provide a link between the early specification and later differentiation of the eye disk.

L4 ANSWER 58 OF 75 CAPLUS COPYRIGHT 2003 ACS on STN
AN 1998:676577 CAPLUS
DN 130:48579
TI The teratogenic Veratrum alkaloid cyclopamine inhibits Sonic hedgehog signal transduction

AU Incardona, John P.; Gaffield, William; Kapur, Raj P.; Roelink, Henk
CS Department of Pediatrics, University of Washington, Seattle, WA, 98195, USA
SO Development (Cambridge, United Kingdom) (1998), 125(18), 3553-3562
CODEN: DEVPED; ISSN: 0950-1991
PB Company of Biologists Ltd.
DT Journal
LA English
AB The steroidal alkaloid cyclopamine produces cyclopia and holoprosencephaly when administered to gastrulation-stage amniote embryos. Cyclopamine-induced malformations in chick embryos are assocd. with interruption of Sonic **hedgehog** (Shh)-mediated dorsoventral patterning of the neural tube and somites. Cell types **normally** induced in the ventral neural tube by Shh are either absent or appear aberrantly at the ventral midline after cyclopamine treatment, while dorsal cell types **normally** repressed by Shh appear ventrally. Somites in cyclopamine-treated embryos show Pax7 expression throughout, indicating failure of sclerotome induction. Cyclopamine at concns. of 20-100 nM blocks the response of neural plate explants to recombinant Shh-N in a dose-dependent manner. Similar concns. have no effect on the post-translational modification of Shh by cholesterol in transfected COS-1 cells. Comparison of the effects of cyclopamine to those of the holoprosencephaly-inducing cholesterol synthesis **inhibitor** AY-9944 shows that cyclopamine does not induce malformations by interfering with cholesterol metab. Although AY-9944 does not interrupt Shh signaling in ovo, it blocks the response to Shh-N in explants cultured without an exogenous cholesterol source. As predicted by current models of the regulation of cholesterol metab., the response to Shh-N in AY-9944-treated explants is restored by providing exogenous cholesterol. However, exogenous cholesterol does not restore Shh signaling in cyclopamine-treated explants. These findings suggest that cyclopamine-induced teratogenesis is due to a more direct antagonism of Shh signal transduction.
RE.CNT 60 THERE ARE 60 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT
AB The steroidal alkaloid cyclopamine produces cyclopia and holoprosencephaly when administered to gastrulation-stage amniote embryos. Cyclopamine-induced malformations in chick embryos are assocd. with interruption of Sonic **hedgehog** (Shh)-mediated dorsoventral patterning of the neural tube and somites. Cell types **normally** induced in the ventral neural tube by Shh are either absent or appear aberrantly at the ventral midline after cyclopamine treatment, while dorsal cell types **normally** repressed by Shh appear ventrally. Somites in cyclopamine-treated embryos show Pax7 expression throughout, indicating failure of sclerotome induction. Cyclopamine at concns. of 20-100 nM blocks the response of neural plate explants to recombinant Shh-N in a dose-dependent manner. Similar concns. have no effect on the post-translational modification of Shh by cholesterol in transfected COS-1 cells. Comparison of the effects of cyclopamine to those of the holoprosencephaly-inducing cholesterol synthesis **inhibitor** AY-9944 shows that cyclopamine does not induce malformations by interfering with cholesterol metab. Although AY-9944 does not interrupt Shh signaling in ovo, it blocks the response to Shh-N in explants cultured without an exogenous cholesterol source. As predicted by current models of the regulation of cholesterol metab., the response to Shh-N in AY-9944-treated explants is restored by providing exogenous cholesterol. However, exogenous cholesterol does not restore Shh signaling in cyclopamine-treated explants. These findings suggest that cyclopamine-induced teratogenesis is due to a more direct antagonism of

Shh signal transduction.

L4 ANSWER 59 OF 75 CAPLUS COPYRIGHT 2003 ACS on STN
AN 1998:345290 CAPLUS
DN 129:105064
TI Expression of wingless in the drosophila embryo: a conserved cis-acting element lacking conserved ci-binding sites is required for patched-mediated repression
AU Lessing, Derek; Nusset, Roel
CS Howard Hughes Medical Institute, Department of Developmental Biology, Beckman Center, Stanford University, Medical Center, Stanford, CA, 94305, USA
SO Development (Cambridge, United Kingdom) (1998), 125(8), 1469-1476
CODEN: DEVPED; ISSN: 0950-1991
PB Company of Biologists Ltd.
DT Journal
LA English
AB Patterning of the Drosophila embryo depends on the accurate expression of wingless (wg). which encodes a secreted signal required for segmentation and many other processes. Early expression of wg is regulated by the nuclear proteins of the gap and pair-rule gene classes but, after gastrulation. wg transcription is also dependent on cell-cell communication. Signaling to the Wg-producing cells is mediated by the secreted protein, **Hedgehog** (Hh), and by Cubitus interruptus (Ci), a transcriptional effector of the Hh signal transduction pathway. The transmembrane protein Patched (Ptc) acts as a neg. regulator of wg expression; ptc- embryos have ectopic wg expression. According to the current models, Ptc is a receptor for Hh. The default activity of Ptc is to **inhibit** Ci function; when Ptc binds Hh, this **inhibition** is released and Ci can control wg transcription. The authors have investigated cis-acting sequences that regulate wg during the time that wg expression depends on Hh signaling. The authors show that approx. 4.5 kb immediately upstream of the wg transcription unit can direct expression of the reporter gene lacZ in domains similar to the **normal** wg pattern in the embryonic ectoderm. Expression of this reporter construct expands in ptc mutants and responds to hh activity. Within this 4.5 kb, a 150 bp element, highly conserved between D. melanogaster and Drosophila virilis, is required to spatially restrict wg transcription. Activity of this element depends on ptc, but it contains no consensus Ci-binding sites. The discovery of an element that is likely to bind a transcriptional repressor was unexpected, since the prevailing model suggests that wg expression is principally controlled by Hh signaling acting through the Ci activator. We show that wg regulatory DNA can drive lacZ in a proper wg-like pattern without any conserved Ci-binding sites and suggest that Ci can not be the sole endpoint of the Hh pathway.
RE.CNT 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT
AB Patterning of the Drosophila embryo depends on the accurate expression of wingless (wg). which encodes a secreted signal required for segmentation and many other processes. Early expression of wg is regulated by the nuclear proteins of the gap and pair-rule gene classes but, after gastrulation. wg transcription is also dependent on cell-cell communication. Signaling to the Wg-producing cells is mediated by the secreted protein, **Hedgehog** (Hh), and by Cubitus interruptus (Ci), a transcriptional effector of the Hh signal transduction pathway. The transmembrane protein Patched (Ptc) acts as a neg. regulator of wg expression; ptc- embryos have ectopic wg expression. According to the current models, Ptc is a receptor for Hh. The default activity of Ptc is

to **inhibit** Ci function; when Ptc binds Hh, this **inhibition** is released and Ci can control wg transcription. The authors have investigated cis-acting sequences that regulate wg during the time that wg expression depends on Hh signaling. The authors show that approx. 4.5 kb immediately upstream of the wg transcription unit can direct expression of the reporter gene lacZ in domains similar to the **normal** wg pattern in the embryonic ectoderm. Expression of this reporter construct expands in ptc mutants and responds to hh activity. Within this 4.5 kb, a 150 bp element, highly conserved between D. melanogaster and Drosophila virilis, is required to spatially restrict wg transcription. Activity of this element depends on ptc, but it contains no consensus Ci-binding sites. The discovery of an element that is likely to bind a transcriptional repressor was unexpected, since the prevailing model suggests that wg expression is principally controlled by Hh signaling acting through the Ci activator. We show that wg regulatory DNA can drive lacZ in a proper wg-like pattern without any conserved Ci-binding sites and suggest that Ci can not be the sole endpoint of the Hh pathway.

L4 ANSWER 60 OF 75 CAPLUS COPYRIGHT 2003 ACS on STN
AN 1998:336818 CAPLUS
DN 129:91227
TI Noggin-mediated antagonism of BMP signaling is required for growth and patterning of the neural tube and somite
AU Mcmahon, Jill A.; Takada, Shinji; Zimmerman, Lyle B.; Fan, Chen-Ming; Harland, Richard M.; Mcmahon, Andrew P.
CS Department of Molecular and Cellular Biology, Harvard University, Cambridge, MA, 02138, USA
SO Genes & Development (1998), 12(10), 1438-1452
CODEN: GEDEEP; ISSN: 0890-9369
PB Cold Spring Harbor Laboratory Press
DT Journal
LA English
AB Embryonic patterning in vertebrates is dependent upon the balance of inductive signals and their specific antagonists. We show that Noggin, which encodes a bone morphogenetic protein (BMP) antagonist expressed in the node, notochord, and dorsal somite, is required for **normal** mouse development. Although Noggin has been implicated in neural induction, examn. of null mutants in the mouse indicates that Noggin is not essential for this process. However, Noggin is required for subsequent growth and patterning of the neural tube. Early BMP-dependent dorsal cell fates, the roof plate and neural crest, form in the absence of Noggin. However, there is a progressive loss of early, Sonic **hedgehog** (Shh)-dependent ventral cell fates despite the **normal** expression of Shh in the notochord. Further, somite differentiation is deficient in both muscle and sclerotomal precursors. Addn. of BMP2 or BMP4 to paraxial mesoderm explants blocks Shh-mediated induction of Pax-1, a sclerotomal marker, whereas addn. of Noggin is sufficient to induce Pax-1. Noggin and Shh induce Pax-1 synergistically. Use of protein kinase A stimulators blocks Shh-mediated induction of Pax-1, but not induction by Noggin, suggesting that induction is mediated by different pathways. Together these data demonstrate that **inhibition** of BMP signaling by axially secreted Noggin is an important requirement for **normal** patterning of the vertebrate neural tube and somite.
RE.CNT 77 THERE ARE 77 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT
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which encodes a bone morphogenetic protein (BMP) antagonist expressed in the node, notochord, and dorsal somite, is required for **normal** mouse development. Although Noggin has been implicated in neural induction, examn. of null mutants in the mouse indicates that Noggin is not essential for this process. However, Noggin is required for subsequent growth and patterning of the neural tube. Early BMP-dependent dorsal cell fates, the roof plate and neural crest, form in the absence of Noggin. However, there is a progressive loss of early, Sonic **hedgehog** (Shh)-dependent ventral cell fates despite the **normal** expression of Shh in the notochord. Further, somite differentiation is deficient in both muscle and sclerotomal precursors. Addn. of BMP2 or BMP4 to paraxial mesoderm explants blocks Shh-mediated induction of Pax-1, a sclerotomal marker, whereas addn. of Noggin is sufficient to induce Pax-1. Noggin and Shh induce Pax-1 synergistically. Use of protein kinase A stimulators blocks Shh-mediated induction of Pax-1, but not induction by Noggin, suggesting that induction is mediated by different pathways. Together these data demonstrate that **inhibition** of BMP signaling by axially secreted Noggin is an important requirement for **normal** patterning of the vertebrate neural tube and somite.

L4 ANSWER 61 OF 75 CAPLUS COPYRIGHT 2003 ACS on STN
AN 1998:40072 CAPLUS
DN 128:163453
TI Activating Smoothened mutations in sporadic basal-cell carcinoma
AU Xie, Jingwu; Murone, Maximilien; Luoh, Shiuh-Ming; Ryan, Anne; Gu, Qimin; Zhang, Chaohui; Bonifas, Jeannette M.; Lam, Ching-Wan; Hynes, Mary; Goddard, Audrey; Rosenthal, Arnon; Epstein, Ervin H., Jr.; de Sauvage, Frederic J.
CS Dep. Dermatology, San Francisco General Hospital, Univ. California, San Franisco, CA, 94110, USA
SO Nature (London) (1998), 391(6662), 90-92
CODEN: NATUAS; ISSN: 0028-0836
PB Macmillan Magazines
DT Journal
LA English
AB Basal-cell carcinomas (BCCs) are the commonest human cancer. Insight into their genesis came from identification of mutations in the PATCHED gene (PTCH) in patients with the basal-cell nevus syndrome, a hereditary disease characterized by multiple BCCs and by developmental abnormalities. The binding of Sonic **hedgehog** (SHH) to its receptor, PTCH, is thought to prevent **normal inhibition** by PTCH of Smoothened (SMO), a seven-span transmembrane protein. According to this model, the **inhibition** of SMO signaling is relieved following mutational inactivation of PTCH in basal-cell nevus syndrome. Here is reported the identification of activating somatic missense mutations in the SMO gene itself in sporadic BCCs from three patients. Mutant SMO, unlike wild type, can cooperate with adenovirus E1A to transform rat embryonic fibroblast cells in culture. Furthermore, skin abnormalities similar to BCCs developed in transgenic murine skin overexpressing mutant SMO. These findings support the role of SMO as a signaling component of the SHH-receptor complex and provide direct evidence that mutated SMO can function as an oncogene in BCCs.
RE.CNT 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT
AB Basal-cell carcinomas (BCCs) are the commonest human cancer. Insight into their genesis came from identification of mutations in the PATCHED gene (PTCH) in patients with the basal-cell nevus syndrome, a hereditary disease characterized by multiple BCCs and by developmental abnormalities.

The binding of Sonic **hedgehog** (SHH) to its receptor, PTCH, is thought to prevent **normal inhibition** by PTCH of Smoothened (SMO), a seven-span transmembrane protein. According to this model, the **inhibition** of SMO signaling is relieved following mutational inactivation of PTCH in basal-cell nevus syndrome. Here is reported the identification of activating somatic missense mutations in the SMO gene itself in sporadic BCCs from three patients. Mutant SMO, unlike wild type, can cooperate with adenovirus E1A to transform rat embryonic fibroblast cells in culture. Furthermore, skin abnormalities similar to BCCs developed in transgenic murine skin overexpressing mutant SMO. These findings support the role of SMO as a signaling component of the SHH-receptor complex and provide direct evidence that mutated SMO can function as an oncogene in BCCs.

L4 ANSWER 62 OF 75 CAPLUS COPYRIGHT 2003 ACS on STN
AN 1997:729328 CAPLUS
DN 128:32637
TI Smoothened-mediated Hedgehog signaling is required for the maintenance of the anterior-posterior lineage restriction in the developing wing of Drosophila
AU Blair, Seth S.; Ralston, Amy
CS Department of Zoology, University of Wisconsin, Madison, WI, 53706, USA
SO Development (Cambridge, United Kingdom) (1997), 124(20), 4053-4063
CODEN: DEVPED; ISSN: 0950-1991
PB Company of Biologists
DT Journal
LA English
AB It is thought that the posterior expression of the "selector" genes engrailed and invected control the subdivision of the growing wing imaginal disk of Drosophila into anterior and posterior lineage compartments. At present, the cellular mechanisms by which sep. lineage compartments are maintained are not known. Most models have assumed that the presence or absence of selector gene expression autonomously drives the expression of compartment-specific adhesion or recognition mols. that **inhibit** intermixing between compartments. However, our present understanding of **Hedgehog** signaling from posterior to anterior cells raises some interesting alternative models based on a cell's response to signaling. We show here that anterior cells that lack smoothened, and thus the ability to receive the **Hedgehog** signal, no longer obey a lineage restriction in the **normal** position of the anterior-posterior boundary. Rather these clones extend into anatomically posterior territory, without any changes in engrailed/invected gene expression. We have also examd. clones lacking both en and inv; these too show complex behaviors near the **normal** site of the compartment boundary, and do not always cross entirely into anatomically anterior territory. Our results suggest that compartmentalization is a complex process involving intercompartmental signaling; models based on changes in affinity or growth will be discussed.
RE.CNT 66 THERE ARE 66 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT
AB It is thought that the posterior expression of the "selector" genes engrailed and invected control the subdivision of the growing wing imaginal disk of Drosophila into anterior and posterior lineage compartments. At present, the cellular mechanisms by which sep. lineage compartments are maintained are not known. Most models have assumed that the presence or absence of selector gene expression autonomously drives the expression of compartment-specific adhesion or recognition mols. that **inhibit** intermixing between compartments. However, our present

understanding of **Hedgehog** signaling from posterior to anterior cells raises some interesting alternative models based on a cell's response to signaling. We show here that anterior cells that lack smoothened, and thus the ability to receive the **Hedgehog** signal, no longer obey a lineage restriction in the **normal** position of the anterior-posterior boundary. Rather these clones extend into anatomically posterior territory, without any changes in engrailed/invected gene expression. We have also examd. clones lacking both en and inv; these too show complex behaviors near the **normal** site of the compartment boundary, and do not always cross entirely into anatomically anterior territory. Our results suggest that compartmentalization is a complex process involving intercompartmental signaling; models based on changes in affinity or growth will be discussed.

L4 ANSWER 63 OF 75 CAPLUS COPYRIGHT 2003 ACS on STN
AN 1997:689397 CAPLUS
DN 127:357708
TI Expression of a truncated, kinase-defective TGF-.beta. type II receptor in mouse skeletal tissue promotes terminal chondrocyte differentiation and osteoarthritis
AU Serra, Rosa; Johnson, Mahlon; Filvaroff, Ellen H.; Laborde, James; Sheehan, Daniel M.; Derynck, Rik; Moses, Harold L.
CS Department of Cell Biology and the Vanderbilt Cancer Center, Vanderbilt University, Nashville, TN, 37232, USA
SO Journal of Cell Biology (1997), 139(2), 541-552
CODEN: JCLBA3; ISSN: 0021-9525
PB Rockefeller University Press
DT Journal
LA English
AB Members of the TGF-.beta. superfamily are important regulators of skeletal development. TGF-.beta.s signal through heteromeric type I and type II receptor serine/threonine kinases. When over-expressed, a cytoplasmically truncated type II receptor can compete with the endogenous receptors for complex formation, thereby acting as a dominant-neg. mutant (DNIIR). To det. the role of TGF-.beta.s in the development and maintenance of the skeleton, the authors have generated transgenic mice (MT-DNIIR-4 and -27) that express the DNIIR in skeletal tissue. DNIIR mRNA expression was localized to the periosteum/perichondrium, synovium, and articular cartilage. Lower levels of DNIIR mRNA were detected in growth plate cartilage. Transgenic mice frequently showed bifurcation of the xiphoid process and sternum. They also developed progressive skeletal degeneration, resulting by 4 to 8 mo of age in kyphoscoliosis and stiff and torqued joints. The histol. of affected joints strongly resembled human osteoarthritis. The articular surface was replaced by bone or hypertrophic cartilage as judged by the expression of type X collagen, a marker of hypertrophic cartilage **normally** absent from articular cartilage. The synovium was hyperplastic, and cartilaginous metaplasia was obsd. in the joint space. The authors then tested the hypothesis that TGF-.beta. is required for **normal** differentiation of cartilage in vivo. By 4 and 8 wk of age, the level of type X collagen was increased in growth plate cartilage of transgenic mice relative to wild-type controls. Less proteoglycan staining was detected in the growth plate and articular cartilage matrix of transgenic mice. Mice that express DNIIR in skeletal tissue also demonstrated increased Indian **hedgehog** (IHH) expression. IHH is a secreted protein that is expressed in chondrocytes that are committed to becoming hypertrophic. It is thought to be involved in a feedback loop that signals through the periosteum/perichondrium to **inhibit** cartilage differentiation.

The data suggest that TGF-.beta. may be crit. for multifaceted maintenance of synovial joints. Loss of responsiveness to TGF-.beta. promotes chondrocyte terminal differentiation and results in development of degenerative joint disease resembling osteoarthritis in humans.

AB Members of the TGF-.beta. superfamily are important regulators of skeletal development. TGF-.beta.s signal through heteromeric type I and type II receptor serine/threonine kinases. When over-expressed, a cytoplasmically truncated type II receptor can compete with the endogenous receptors for complex formation, thereby acting as a dominant-neg. mutant (DNIIR). To det. the role of TGF-.beta.s in the development and maintenance of the skeleton, the authors have generated transgenic mice (MT-DNIIR-4 and -27) that express the DNIIR in skeletal tissue. DNIIR mRNA expression was localized to the periosteum/perichondrium, synovium, and articular cartilage. Lower levels of DNIIR mRNA were detected in growth plate cartilage. Transgenic mice frequently showed bifurcation of the xiphoid process and sternum. They also developed progressive skeletal degeneration, resulting by 4 to 8 mo of age in kyphoscoliosis and stiff and torqued joints. The histol. of affected joints strongly resembled human osteoarthritis. The articular surface was replaced by bone or hypertrophic cartilage as judged by the expression of type X collagen, a marker of hypertrophic cartilage **normally** absent from articular cartilage. The synovium was hyperplastic, and cartilaginous metaplasia was obsd. in the joint space. The authors then tested the hypothesis that TGF-.beta. is required for **normal** differentiation of cartilage in vivo. By 4 and 8 wk of age, the level of type X collagen was increased in growth plate cartilage of transgenic mice relative to wild-type controls. Less proteoglycan staining was detected in the growth plate and articular cartilage matrix of transgenic mice. Mice that express DNIIR in skeletal tissue also demonstrated increased Indian **hedgehog** (IHH) expression. IHH is a secreted protein that is expressed in chondrocytes that are committed to becoming hypertrophic. It is thought to be involved in a feedback loop that signals through the periosteum/perichondrium to **inhibit** cartilage differentiation. The data suggest that TGF-.beta. may be crit. for multifaceted maintenance of synovial joints. Loss of responsiveness to TGF-.beta. promotes chondrocyte terminal differentiation and results in development of degenerative joint disease resembling osteoarthritis in humans.

L4 ANSWER 64 OF 75 CAPLUS COPYRIGHT 2003 ACS on STN
AN 1997:645783 CAPLUS
DN 127:317455
TI Involvement of Sonic hedgehog in the cell growth of LK-2 cells, human lung squamous carcinoma cells
AU Fujita, Eriko; Khoroku, Yoriko; Urase, Koko; Tsukahara, Toshifumi; Momoi, Mariko Y.; Kumagai, Hiromichi; Takemura, Tamiko; Kuroki, Toshio; Momoi, Takashi
CS Division of Development and Differentiation, National Institute of Neuroscience, NCNP, Kodaira, 187, Japan
SO Biochemical and Biophysical Research Communications (1997), 238(2), 658-664
CODEN: BBRCA9; ISSN: 0006-291X
PB Academic
DT Journal
LA English
AB Mutation of the Patched gene has been detected in human inherited basal cell nevus syndrome (BCNS) and sporadic basal cell carcinomas (BCC), suggesting a strong relation between a Sonic **hedgehog**-Patched signal and cell proliferation. In the present study, the authors demonstrate that Sonic **hedgehog** is expressed in human lung

squamous carcinoma (LK-2 and EBC-1) and some adenocarcinoma cell lines. The expression of Sonic **hedgehog** is also detected in the human lung squamous carcinoma tissues, but not in the **normal** lung tissue of the same patient. The N-terminal region of Sonic **hedgehog** stimulates the incorporation of BrdU into LK-2 cells and stimulates their cell growth, while anti-Shh-N **inhibits** their cell growth. These results suggest that a Sonic **hedgehog** signal is involved in the cell growth of LK-2 cells.

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L4 ANSWER 65 OF 75 CAPLUS COPYRIGHT 2003 ACS on STN
AN 1997:594414 CAPLUS
TI Left/right patterning signals and the independent regulation of different aspects of situs in the chick embryo
AU Levin, Michael; Pagan, Sylvia; Roberts, Drucilla J.; Cooke, Jonathan; Kuehn, Michael R.; Tabin, Clifford J.
CS Department of Genetics, Harvard Medical School, Boston, MA, 02115, USA
SO Developmental Biology (1997), 189(1), 57-67
CODEN: DEBIAO; ISSN: 0012-1606
PB Academic
DT Journal
LA English
AB Recently, a pathway of genes which are part of a cascade regulating the side on which the heart forms during chick development was characterized (M. Levin et al., 1995, Cell 82, 1-20). Here we extend these previous studies, showing that manipulation of at least one member of the cascade, Sonic **hedgehog** (Shh), can affect the situs of embryonic rotation and of the gut, in addn. to the heart. Bilateral expression of Shh, which is **normally** found exclusively on the left, does not result in left isomerism (a bilaterally sym. embryo having two left sides) nor in a complete situs inversus phenotype. Instead, misexpression of Shh on the right side of the node, which in turn leads to bilateral nodal expression, produces a heterotaxia-like condition, where different aspects of laterality are detd. independently. Heart situs has previously been shown to be altered by ectopic Shh and activin. However, the most downstream gene identified in the LR pathway, nodal, had not been functionally linked to heart laterality. We show that ectopic (right-sided) nodal expression is able to affect heart situs, suggesting that the randomization of heart laterality obsd. in Shh and activin misexpression expts. is a result of changes in nodal expression and that nodal is likely to regulate heart situs endogenously. The first defined asym. signal in the left-right patterning pathway is Shh, which is initially expressed throughout Hensen's node but becomes restricted to the left side at stage 4+. It has been hypothesized that the restriction of Shh expression may be due to repression by an upstream activin-like factor. The involvement of such an activin-like factor on the right side of Hensen's node was suggested because ectopic activin protein is able to repress Shh on the left side of

the node, as well as to induce ectopic expression of a **normally** right-sided marker, the activin receptor cAct-RIIa. Here we provide further evidence in favor of this model. We find that a member of this family, Activin .beta.B, is indeed expressed asym., only on the right side of Hensen's node, at the correct time for it to be the endogenous asym. activin signal. Furthermore, we show that application of follistatin-loaded beads eliminates the asymmetry in Shh expression, consistent with an **inhibition** of an endogenous member of the activin-BMP superfamily. This combined with the previous data on exogenous activin supports the model that Activin .beta.B functions in the chick embryo to initiate Shh asymmetry. While these data extend our understanding of the early signals which establish left-right asymmetry, they leave unanswered the interesting question of how the bilateral symmetry of the embryo is initially broken to define a consistent left-right axis. Anal. of spontaneous chick twins suggests that, whatever the mol. mechanism, left-right patterning is unlikely to be due to a blastodermal prepattern but rather is initiated in a streak-autonomous manner.

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L4 ANSWER 66 OF 75 CAPLUS COPYRIGHT 2003 ACS on STN
AN 1997:254649 CAPLUS
DN 126:249514
TI Cholesterol and development
AU Roux, charles; Wolf, Claude; Llirbat, Beatrice; Kolf, Martine; Mulliez, Nicole; Taillemite, Jean-Louis; Cormier, Valerie; Le Merrer, Martine; Chevy, Francoise; Citadelle, Daniele
CS Laboratoire d'Embryologie Pathologique Experimentale, CHU Saint-Antoine, Paris, Fr.
SO Comptes Rendus des Seances de la Societe de Biologie et de Ses Filiales (1997), 191(1), 113-123
CODEN: CRSBAW; ISSN: 0037-9026
PB Masson
DT Journal; General Review
LA French
AB A review with 19 refs. The teratogenic action of distal **inhibitors** of cholesterol synthesis has been known for some time. The induced malformations are of a particular type: they include holoprosenecephalics. Recently, these observations have solicited increased interest due to: (1) the discovery in 1993 of a similar form of **inhibition** of cholesterol synthesis which is responsible for a human malformation syndrome (Smith-Lemli-Opitz); and (2) the demonstration of the involvement of the Sonic **Hedgehog** gene in the **normal** development of the prosencephalon and the description of the mode of action of protein Sbh; autoprocessing followed by cholesterolization.
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L4 ANSWER 67 OF 75 CAPLUS COPYRIGHT 2003 ACS on STN
AN 1997:181898 CAPLUS
DN 126:223137
TI Role of decapentaplegic initiation and progression of the morphogenetic furrow in the developing Drosophila retina
AU Chanut, Francoise; Heberlein, Ulrike
CS Gallo Center Dep. Neurology, Univ. California, San Francisco, CA, 94110, USA
SO Development (Cambridge, United Kingdom) (1997), 124(2), 559-567
CODEN: DEVPED; ISSN: 0950-1991
PB Company of Biologists
DT Journal
LA English
AB Morphogenesis in the Drosophila retina initiates at the posterior margin of the eye imaginal disk by an unknown mechanism. Upon initiation, a wave of differentiation, its forward edge marked by the morphogenetic furrow (MF) is driven by **hedgehog** (hh), expressed by differentiating photoreceptor cells. The TGF-.beta. homolog encoded by decapentaplegic

(dpp) is expressed at the disk's posterior margin prior to initiation and in the furrow, under the control of hh, during MF progression. While dpp has been implicated in eye disk growth and morphogenesis, its precise role in retinal differential has not been detd. To address the role of dpp in initiation and progression of retinal differentiation the authors analyzed the consequences of reduced and increased dpp function during eye development. The authors find that dpp is not only required for **normal** MF initiation, but is sufficient to induce ectopic initiation of differentiation. Inappropriate initiation is **normally inhibited** by wingless (wg). Loss of dpp function is accompanied by expansion of wg expression, while increased dpp function leads to loss of wg transcription. In addn., dpp is required to maintain, and sufficient to induce, its own expression along the disk's margins. The authors postulate that dpp autoregulation and dpp-mediated **inhibition** of wg expression are required for the coordinated regulation of furrow initiation and progression. Finally, the authors show that in the later stages of retinal differentiation, redn. of dpp function leads to an arrest in MF progression.

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L4 ANSWER 68 OF 75 CAPLUS COPYRIGHT 2003 ACS on STN
AN 1997:75434 CAPLUS
DN 126:155512
TI Involvement of Sonic hedgehog (Shh) in mouse embryonic lung growth and morphogenesis
AU Bellusci, Saverio; Furuta, Yasuhide; Rush, Margaret G.; Henderson, Randall; Winnier, Glenn; Hogan, Brigid L. M.
CS Vanderbilt University Medical Center, Howard Hughes Medical Institute, Nashville, TN, 37232-2175, USA
SO Development (Cambridge, United Kingdom) (1997), 124(1), 53-63
CODEN: DEVPED; ISSN: 0950-1991
PB Company of Biologists
DT Journal
LA English
AB Branching morphogenesis of the embryonic lung requires interactions between the epithelium and the mesenchyme. Previously, we reported that Sonic **hedgehog** (Shh) transcripts are present in the epithelium

of the developing mouse lung, with highest levels in the terminal buds. Here, we report that transcripts of mouse patched (Ptc), the homolog of a Drosophila gene encoding a putative transmembrane protein required for **hedgehog** signaling, are expressed at high levels in the mesenchyme adjacent to the end buds. To investigate the function of SHH in lung development, Shh was overexpressed throughout the distal epithelium, using the surfactant protein-C (SP-C)-enhancer/promoter. Beginning around 16.5 dpc, when Shh and Ptc RNA levels are **normally** both declining, this treatment caused an increase in the ratio of interstitial mesenchyme to epithelial tubules in transgenic compared to **normal** lungs. Transgenic newborn mice die soon after birth. Histol. anal. of the lungs at the light and electron microscope level shows an abundance of mesenchyme and the absence of typical alveoli. In vivo BrdU labeling indicates that Shh overexpression results in increased mesenchymal and epithelial cell proliferation at 16.5 and 17.5 dpc. However, anal. of CC-10 and SP-C expression reveals no significant **inhibition** in the differentiation of proximal and distal epithelial cells. The expression of genes potentially regulated by SHH was also examd. No difference could be obsd. between transgenic and control lungs in either the level or distribution of Bmp4, Wnt2 and Fgf7 RNA. By contrast, Ptc is clearly upregulated in the transgenic lung. These results thus establish a role for SHH in lung morphogenesis, and suggest that SHH **normally** regulates lung mesenchymal cell proliferation in vivo.

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L4 ANSWER 69 OF 75 CAPLUS COPYRIGHT 2003 ACS on STN
AN 1996:668482 CAPLUS
TI Restoration of the organizer after radical ablation of Hensen's node and the anterior primitive streak in the chick embryo
AU Psychoyos, Delphine; Stern, Claudio D.
CS Dep. Genetics and Dev., Columbia Univ., New York, NY, 10032, USA
SO Development (Cambridge, United Kingdom) (1996), 122(10), 3263-3273
CODEN: DEVPED; ISSN: 0950-1991
PB Company of Biologists

DT Journal
LA English
AB The region of the amniote embryo corresponding to Spemann's organizer in amphibians is Hensen's node, which lies at the tip of the primitive streak during gastrulation. It is a special site in the embryo that can be defined by the presence of progenitors of several axial tissues (notochord, prechordal mesoderm, somites, gut endoderm), by characteristic cell movements, by specific patterns of gene expression (e.g. goosecoid, HNF-3.beta., Sonic **hedgehog**) and, most importantly, by its ability to induce a complete axis, including host-derived neural tissue, when transplanted to an ectopic site. Here, we show that complete removal not only of the node but also of the anterior 40% of the primitive streak leads to the development of **normal** embryos contg. cells with all the fates **normally** produced by the node. Cell movement pathways through the regenerated node are identical to those seen in the **normal** embryo. The patterns of expression of HNF-3.beta. and Sonic **hedgehog** are also restored, as is their left/right asymmetry, but goosecoid expression is not. When the regenerated node is transplanted to an ectopic site, it induces a complete embryonic axis that includes a fully patterned, host-derived central nervous system. Anal. of the properties of cell surrounding the site of ablation shows that they acquire these properties gradually. We suggest that the organizer is a region of the embryo that is defined by cell interactions and that the node **normally inhibits** the organize state in neighboring cells.
AB The region of the amniote embryo corresponding to Spemann's organizer in amphibians is Hensen's node, which lies at the tip of the primitive streak during gastrulation. It is a special site in the embryo that can be defined by the presence of progenitors of several axial tissues (notochord, prechordal mesoderm, somites, gut endoderm), by characteristic cell movements, by specific patterns of gene expression (e.g. goosecoid, HNF-3.beta., Sonic **hedgehog**) and, most importantly, by its ability to induce a complete axis, including host-derived neural tissue, when transplanted to an ectopic site. Here, we show that complete removal not only of the node but also of the anterior 40% of the primitive streak leads to the development of **normal** embryos contg. cells with all the fates **normally** produced by the node. Cell movement pathways through the regenerated node are identical to those seen in the **normal** embryo. The patterns of expression of HNF-3.beta. and Sonic **hedgehog** are also restored, as is their left/right asymmetry, but goosecoid expression is not. When the regenerated node is transplanted to an ectopic site, it induces a complete embryonic axis that includes a fully patterned, host-derived central nervous system. Anal. of the properties of cell surrounding the site of ablation shows that they acquire these properties gradually. We suggest that the organizer is a region of the embryo that is defined by cell interactions and that the node **normally inhibits** the organize state in neighboring cells.

L4 ANSWER 70 OF 75 CAPLUS COPYRIGHT 2003 ACS on STN
AN 1996:584700 CAPLUS
DN 125:270934
TI The expression and regulation of follistatin and a follistatin-like gene during avian somite compartmentalization and myogenesis
AU Amthor, Helge; Connolly, David; Patel, Ketan; Brand-Saberi, Beate; Wilkinson, David G.; Cooke, Jonathan; Christ, Bodo
CS Institute Anatomy, Univ. Freiburg, Freiburg, D-79001, Germany
SO Developmental Biology (1996), 178(2), 343-362
CODEN: DEBIAO; ISSN: 0012-1606

PB Academic
DT Journal
LA English
AB The authors report on the **normal** and exptl. altered expression of 2 structurally related genes, Follistatin and Follistatin-like (Flik), in the somites of avian embryos. In **normal** chick embryos, Follistatin expression can first be seen in the cells of the dorsolateral somite quarter. During somite maturation, the cells of the dorsomedial quarter also express this gene. Within the dermomyotome it seems that only the muscle precursors are Follistatin-pos. The migrating precursors of limb and tongue muscle as well as the myotome cells show Follistatin expression. The manipulation expts. reveal that the expression of Follistatin in the somites can be **inhibited** by notochord signals. This effect can be mimicked by sonic **hedgehog** protein. Flik is expressed in the dorsomedial component of the somite and later on in the myotome. Unlike Follistatin, Flik expression requires signals emanating from the neural tube. Notochordal influences do not alter Flik expression. The expression of both genes does not depend on signals of intermediate or lateral mesoderm. Since the products of both genes are proposed to antagonize TGF-.beta. superfamily proteins during gastrulation and neuralization, the authors postulate that during myogenesis follistatin and flik counteract **inhibiting** effects of related mols. on muscle differentiation.
AB The authors report on the **normal** and exptl. altered expression of 2 structurally related genes, Follistatin and Follistatin-like (Flik), in the somites of avian embryos. In **normal** chick embryos, Follistatin expression can first be seen in the cells of the dorsolateral somite quarter. During somite maturation, the cells of the dorsomedial quarter also express this gene. Within the dermomyotome it seems that only the muscle precursors are Follistatin-pos. The migrating precursors of limb and tongue muscle as well as the myotome cells show Follistatin expression. The manipulation expts. reveal that the expression of Follistatin in the somites can be **inhibited** by notochord signals. This effect can be mimicked by sonic **hedgehog** protein. Flik is expressed in the dorsomedial component of the somite and later on in the myotome. Unlike Follistatin, Flik expression requires signals emanating from the neural tube. Notochordal influences do not alter Flik expression. The expression of both genes does not depend on signals of intermediate or lateral mesoderm. Since the products of both genes are proposed to antagonize TGF-.beta. superfamily proteins during gastrulation and neuralization, the authors postulate that during myogenesis follistatin and flik counteract **inhibiting** effects of related mols. on muscle differentiation.

L4 ANSWER 71 OF 75 CAPLUS COPYRIGHT 2003 ACS on STN
AN 1996:580486 CAPLUS
DN 125:270926
TI Retinoic acid is required for the initiation of outgrowth in the chick limb bud
AU Stratford, Thomas; Horton, Claire; Maden, Malcolm
CS Developmental Biol. Res. Cent., King's Coll., London, WC2B 5RL, UK
SO Current Biology (1996), 6(9), 1124-1133
CODEN: CUBLE2; ISSN: 0960-9822
PB Current Biology
DT Journal
LA English
AB We have investigated the role of endogenous retinoic acid (RA) during chick limb development by preventing the synthesis of RA and testing the effect on various genes expressed during limb initiation and outgrowth.

The stage 20/21 limb bud synthesizes didehydroretinoic acid (ddRA), and the posterior half of the limb bud synthesizes ddRA at a higher rate than the anterior half. Disulfiram **inhibits** this synthesis at micromolar concns. Administering disulfiram to embryos prior to limb bud outgrowth (stages 12-18) abolishes outgrowth, and no limb develops in the majority of cases. Disulfiram treatment also prevents the expression of Sonic **hedgehog** (Shh), but the expression of the fibroblast growth factor-8 gene (Fgf-8) appears as **normal** in the ectoderm over the prospective limb bud. The application of bead soaked in RA can rescue Shh expression. Disulfiram treatment of later limb buds (stages 20-23) similarly down-regulates Shh, and also Fgf-4 expression, whereas the expression of Fgf-8, as at earlier stages, is initially unaffected. Again, RA can rescue the expression of Shh in these limb buds. RA, in conjunction with Fgf-8, may be needed for the induction of the chick limb bud and the induction of Shh and Fgf-4 expression. The expression of Shh and Fgf-4 remains dependent upon the continued synthesis of RA within the limb bud. Didehydroretinoic acid is the major active retinoid in the stage 20 chick limb bud.

AB We have investigated the role of endogenous retinoic acid (RA) during chick limb development by preventing the synthesis of RA and testing the effect on various genes expressed during limb initiation and outgrowth. The stage 20/21 limb bud synthesizes didehydroretinoic acid (ddRA), and the posterior half of the limb bud synthesizes ddRA at a higher rate than the anterior half. Disulfiram **inhibits** this synthesis at micromolar concns. Administering disulfiram to embryos prior to limb bud outgrowth (stages 12-18) abolishes outgrowth, and no limb develops in the majority of cases. Disulfiram treatment also prevents the expression of Sonic **hedgehog** (Shh), but the expression of the fibroblast growth factor-8 gene (Fgf-8) appears as **normal** in the ectoderm over the prospective limb bud. The application of bead soaked in RA can rescue Shh expression. Disulfiram treatment of later limb buds (stages 20-23) similarly down-regulates Shh, and also Fgf-4 expression, whereas the expression of Fgf-8, as at earlier stages, is initially unaffected. Again, RA can rescue the expression of Shh in these limb buds. RA, in conjunction with Fgf-8, may be needed for the induction of the chick limb bud and the induction of Shh and Fgf-4 expression. The expression of Shh and Fgf-4 remains dependent upon the continued synthesis of RA within the limb bud. Didehydroretinoic acid is the major active retinoid in the stage 20 chick limb bud.

L4 ANSWER 72 OF 75 CAPLUS COPYRIGHT 2003 ACS on STN
AN 1996:383952 CAPLUS
DN 125:82758
TI Evidence from normal expression and targeted misexpression that bone morphogenetic protein-4 (Bmp-4) plays a role in mouse embryonic lung morphogenesis
AU Bellusci, Saverio; Henderson, Randall; Winnier, Glenn; Oikawa, Tsuyoshi; Hogan, Brigid L. M.
CS Howard Hughes Medical Inst., Vanderbilt Univ. Medical Center, Nashville, TN, 37232-2175, USA
SO Development (Cambridge, United Kingdom) (1996), 122(6), 1693-1702
CODEN: DEVPED; ISSN: 0950-1991
PB Company of Biologists
DT Journal
LA English
AB Epithelial-mesenchymal interactions are crit. for the branching and differentiation of the lung, but the mechanisms involved are still unclear. To investigate this problem in mouse embryonic lung, we have studied the temporal and spatial expression of genes implicated in the

morphogenesis of other organs. At 11.5 days p.c., hepatocyte nuclear factor-3.beta. (Hnf-3.beta.) is expressed uniformly throughout the epithelium, while Wnt-2 expression is confined to the distal mesenchyme. Sonic **hedgehog** (Shh) transcripts are found throughout the epithelium, with high levels in the distal tips of the terminal buds, while bone morphogenetic protein-4 (Bmp-4) transcripts are localized at high levels in the distal tips of the epithelium, with lower levels in the adjacent mesenchyme. Epithelial expression is also seen for Bmp-7, but transcripts are less dramatically upregulated at the distal tips. The Type I Bone morphogenetic protein receptor gene(Bmpr/Tfr-11/Brk-1) is expressed at low levels in the epithelium and in the distal mesenchyme. To investigate the role of Bmp-4 in lung development, we have misexpressed the gene throughout the distal epithelium of transgenic lungs using a surfactant protein C enhancer/promoter. From 15.5 days p.c., transgenic lungs are smaller than **normal**, with grossly distended terminal buds and, at birth, contain large air-filled sacs which do not support **normal** lung function. Labeling with BrdU reveals an **inhibition** of epithelial proliferation in 15.5 days p.c. transgenic lungs. A small but significant stimulation of proliferation of mesenchymal cells is also obsd., but this is accompanied by an increase in cell death. In situ hybridization with riboprobes for the proximal airway marker, CC10, and the distal airway marker, SP-C, shows **normal** differentiation of bronchiolar Clara cells but a redn. in the no. of differentiated Type II cells in transgenic lungs. A model is proposed for the role of BMP4 and other signalling mols. in embryonic lung morphogenesis.

AB Epithelial-mesenchymal interactions are crit. for the branching and differentiation of the lung, but the mechanisms involved are still unclear. To investigate this problem in mouse embryonic lung, we have studied the temporal and spatial expression of genes implicated in the morphogenesis of other organs. At 11.5 days p.c., hepatocyte nuclear factor-3.beta. (Hnf-3.beta.) is expressed uniformly throughout the epithelium, while Wnt-2 expression is confined to the distal mesenchyme. Sonic **hedgehog** (Shh) transcripts are found throughout the epithelium, with high levels in the distal tips of the terminal buds, while bone morphogenetic protein-4 (Bmp-4) transcripts are localized at high levels in the distal tips of the epithelium, with lower levels in the adjacent mesenchyme. Epithelial expression is also seen for Bmp-7, but transcripts are less dramatically upregulated at the distal tips. The Type I Bone morphogenetic protein receptor gene(Bmpr/Tfr-11/Brk-1) is expressed at low levels in the epithelium and in the distal mesenchyme. To investigate the role of Bmp-4 in lung development, we have misexpressed the gene throughout the distal epithelium of transgenic lungs using a surfactant protein C enhancer/promoter. From 15.5 days p.c., transgenic lungs are smaller than **normal**, with grossly distended terminal buds and, at birth, contain large air-filled sacs which do not support **normal** lung function. Labeling with BrdU reveals an **inhibition** of epithelial proliferation in 15.5 days p.c. transgenic lungs. A small but significant stimulation of proliferation of mesenchymal cells is also obsd., but this is accompanied by an increase in cell death. In situ hybridization with riboprobes for the proximal airway marker, CC10, and the distal airway marker, SP-C, shows **normal** differentiation of bronchiolar Clara cells but a redn. in the no. of differentiated Type II cells in transgenic lungs. A model is proposed for the role of BMP4 and other signalling mols. in embryonic lung morphogenesis.

L4 ANSWER 73 OF 75 CAPLUS COPYRIGHT 2003 ACS on STN
AN 1996:19089 CAPLUS

DN 124:51157
TI Patched overexpression alters wing disk size and pattern: transcriptional and post-transcriptional effects on hedgehog targets
AU Johnson, Ronald L.; Grenier, Jennifer K.; Scott, Matthew P.
CS Howard Hughes Med. Inst., Stanford Univ. Sch. Med., Stanford, CA, 94305-5427, USA
SO Development (Cambridge, United Kingdom) (1995), 121(12), 4161-70
CODEN: DEVPED; ISSN: 0950-1991
PB Company of Biologists
DT Journal
LA English
AB The membrane protein, Patched, plays a crit. role in patterning embryonic and imaginal tissues in Drosophila. Patched constitutively inactivates the transcription of target genes such as wingless, decapentaplegic, and patched itself. The secreted protein, **Hedgehog**, induces transcription of target genes by opposing the Patched signaling pathway. Using the Gal4 UAS system we have overexpressed gene patched in wing imaginal disks and found that high Patched levels, expressed in either **normal** or ectopic patterns, result in loss of wing vein patterning in both compartments centering at the anterior/posterior border. In addn., patched **inhibits** the formation of the mechanosensory neurons, the campaniform sensilla, in the wing blade. The patched wing vein phenotype is modulated by mutations in **hedgehog** and cubitus interruptus (ci). Patched overexpression **inhibits** transcription of patched and decapentaplegic and post-transcriptionally decreases the amt. of Ci protein at the anterior/posterior boundary. In **hedgehogMrt** wing disks, which express ectopic **hedgehog**, Ci levels are correspondingly elevated, suggesting that **hedgehog** relieves patched repression of Ci accumulation. Protein kinase A also regulates Ci; protein kinase A mutant clones in the anterior compartment have increased levels of Ci protein. Thus patched influences wing disk patterning by decreasing Ci protein levels and inactivating **hedgehog** target genes in the anterior compartment.
AB The membrane protein, Patched, plays a crit. role in patterning embryonic and imaginal tissues in Drosophila. Patched constitutively inactivates the transcription of target genes such as wingless, decapentaplegic, and patched itself. The secreted protein, **Hedgehog**, induces transcription of target genes by opposing the Patched signaling pathway. Using the Gal4 UAS system we have overexpressed gene patched in wing imaginal disks and found that high Patched levels, expressed in either **normal** or ectopic patterns, result in loss of wing vein patterning in both compartments centering at the anterior/posterior border. In addn., patched **inhibits** the formation of the mechanosensory neurons, the campaniform sensilla, in the wing blade. The patched wing vein phenotype is modulated by mutations in **hedgehog** and cubitus interruptus (ci). Patched overexpression **inhibits** transcription of patched and decapentaplegic and post-transcriptionally decreases the amt. of Ci protein at the anterior/posterior boundary. In **hedgehogMrt** wing disks, which express ectopic **hedgehog**, Ci levels are correspondingly elevated, suggesting that **hedgehog** relieves patched repression of Ci accumulation. Protein kinase A also regulates Ci; protein kinase A mutant clones in the anterior compartment have increased levels of Ci protein. Thus patched influences wing disk patterning by decreasing Ci protein levels and inactivating **hedgehog** target genes in the anterior compartment.

L4 ANSWER 74 OF 75 CAPLUS COPYRIGHT 2003 ACS on STN
AN 1995:962769 CAPLUS
DN 124:5281

TI Wingless inhibits morphogenetic furrow movement in the Drosophila eye disk
AU Treisman, Jessica E.; Rubin, Gerald M.
CS HHMI and Department of Molecular and Cell Biology, UC Berkeley, Berkeley, CA, 94720, USA
SO Development (Cambridge, United Kingdom) (1995), 121(11), 3519-27
CODEN: DEVPED; ISSN: 0950-1991
PB Company of Biologists
DT Journal
LA English
AB Differentiation of the Drosophila eye imaginal disk is an asynchronous, repetitive process which proceeds across the disk from posterior to anterior. Its propagation correlates with the expression of decapentaplegic at the front of differentiation, in the morphogenetic furrow. Both differentiation and decapentaplegic expression are maintained by **Hedgehog** protein secreted by the differentiated cells posterior to the furrow. However, their initiation at the posterior margin occurs prior to **hedgehog** expression by an unknown mechanism. We show here that the wingless gene contributes to the correct spatial localization of initiation. Initiation of the morphogenetic furrow is restricted to the posterior margin by the presence of wingless at the lateral margins; removal of wingless allows lateral initiation. Ectopic expression of wingless at the posterior margin can also **inhibit normal** initiation. In addn., the presence of wingless in the center of the disk can prevent furrow progression. These effects of wingless are achieved without altering the expression of decapentaplegic.
AB Differentiation of the Drosophila eye imaginal disk is an asynchronous, repetitive process which proceeds across the disk from posterior to anterior. Its propagation correlates with the expression of decapentaplegic at the front of differentiation, in the morphogenetic furrow. Both differentiation and decapentaplegic expression are maintained by **Hedgehog** protein secreted by the differentiated cells posterior to the furrow. However, their initiation at the posterior margin occurs prior to **hedgehog** expression by an unknown mechanism. We show here that the wingless gene contributes to the correct spatial localization of initiation. Initiation of the morphogenetic furrow is restricted to the posterior margin by the presence of wingless at the lateral margins; removal of wingless allows lateral initiation. Ectopic expression of wingless at the posterior margin can also **inhibit normal** initiation. In addn., the presence of wingless in the center of the disk can prevent furrow progression. These effects of wingless are achieved without altering the expression of decapentaplegic.

L4 ANSWER 75 OF 75 CAPLUS COPYRIGHT 2003 ACS on STN
AN 1995:909229 CAPLUS
DN 123:310764
TI Midline signaling is required for Pax gene regulation and patterning of the eyes
AU Macdonald, Rachel; Barth, K. Anukampa; Xu, Qiling; Holder, Nigel; Mikkola, Ingvild; Wilson, Stephen W.
CS Randall Inst., Kings Coll., London, WC2B 5RL, UK
SO Development (Cambridge, United Kingdom) (1995), 121(10), 3267-78
CODEN: DEVPED; ISSN: 0950-1991
PB Company of Biologists
DT Journal
LA English
AB Pax6 and Pax2 are members of the Pax family of transcription factors that are both expressed in the developing visual system of zebrafish embryos.

Pax6 protein is present in all cells that form the neural retina and pigment epithelium, whereas Pax2 is located primarily in cells that will give rise to the optic stalk. In this study, the authors have addressed the role of midline signaling in the regulation of Pax2 and Pax6 distributions and in the subsequent morphogenesis of the eyes. Midline signaling is severely perturbed in cyclops mutant embryos resulting in an absence of ventral midline CNS tissue and fusion of the eyes. Mutant embryos ectopically express Pax6 in a bridge of tissue around the anterior pole of the neural keel in the position **normally** occupied by cells that form the optic stalks. In contrast, Pax2 protein is almost completely absent from this region in mutant embryos. Concomitant with the changes in Pax protein distribution, cells in the position of the optic stalks differentiate as retina. These results suggest that a signal emanating from the midline, which is absent in cyclops mutant embryos, may be required to promote Pax2 and **inhibit** Pax6 expression in cells destined to form the optic stalks. Sonic **hedgehog** (Shh also known as Vhh-1 and Hhg-1) is a midline signaling mol. that is absent from the neuroepithelium of cyclops mutant embryos at early developmental stages. To test the possibility that Shh might be able to regulate the spatial expression of Pax6 and Pax2 in the optic primordia, it was overexpressed in the developing CNS. The no. of cells contg. Pax2 was increased following shh over-expression and embryos developed hypertrophied optic stalk-like structures. Complimentary to the changes in Pax2 distribution, there were fewer Pax6-contg. cells and pigment epithelium and neural retina were reduced. The results suggest that Shh or a closely related signaling mol. emanating from midline tissue in the ventral forebrain either directly or indirectly induces the expression of Pax2 and **inhibits** the expression of Pax6 and thus may regulate the partitioning of the optic primordia into optic stalks and retinal tissue.

AB Pax6 and Pax2 are members of the Pax family of transcription factors that are both expressed in the developing visual system of zebrafish embryos. Pax6 protein is present in all cells that form the neural retina and pigment epithelium, whereas Pax2 is located primarily in cells that will give rise to the optic stalk. In this study, the authors have addressed the role of midline signaling in the regulation of Pax2 and Pax6 distributions and in the subsequent morphogenesis of the eyes. Midline signaling is severely perturbed in cyclops mutant embryos resulting in an absence of ventral midline CNS tissue and fusion of the eyes. Mutant embryos ectopically express Pax6 in a bridge of tissue around the anterior pole of the neural keel in the position **normally** occupied by cells that form the optic stalks. In contrast, Pax2 protein is almost completely absent from this region in mutant embryos. Concomitant with the changes in Pax protein distribution, cells in the position of the optic stalks differentiate as retina. These results suggest that a signal emanating from the midline, which is absent in cyclops mutant embryos, may be required to promote Pax2 and **inhibit** Pax6 expression in cells destined to form the optic stalks. Sonic **hedgehog** (Shh also known as Vhh-1 and Hhg-1) is a midline signaling mol. that is absent from the neuroepithelium of cyclops mutant embryos at early developmental stages. To test the possibility that Shh might be able to regulate the spatial expression of Pax6 and Pax2 in the optic primordia, it was overexpressed in the developing CNS. The no. of cells contg. Pax2 was increased following shh over-expression and embryos developed hypertrophied optic stalk-like structures. Complimentary to the changes in Pax2 distribution, there were fewer Pax6-contg. cells and pigment epithelium and neural retina were reduced. The results suggest that Shh or a closely related signaling mol. emanating from midline tissue in the ventral forebrain either directly or indirectly induces the expression of

Pax2 and **inhibits** the expression of Pax6 and thus may regulate the partitioning of the optic primordia into optic stalks and retinal tissue.